Chapter 1
Barriers of the Human Organism and Their Achilles' Heels

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Contents

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Abstract The human body is covered by barriers separating it from the external and internal surroundings. The "***milieu enterieur***" has to be stabilised in spite of the variable external and internal conditions of toxic, osmotic, microbial and climatic environmental circumstances. This first line of barriers is composed of skin and mucous membranes of complicated structures.

A second line of barrier system is present in our organisms. Certain organs have to be separated from the immune system and other parts of the body because of evolutionary reasons (eye-bulb and testicles) because of unique proteins "unknown" for the acquired immune system. The blood-brain barrier (BBB) is providing enhanced safety circumstances for the central nervous system. The second line of barriers is represented by the special properties of the capillary endothelial system.

The maternal-fetal barrier is the most complex. At the maternal fetal interface two individuals of two different haplotypes has to be live 9 months separated by a very complicated dynamic barrier.

The placenta is the organ, which is separating the maternal and fetal tissues. Similar to others the bidirectional transport of gasses, metabolites, cells, proteins, regulatory substances, are transported by active or passive transcellular and intercellular mechanisms.

The fetal immune system develops immunotolerance to all maternal cells and antigens transferred transplacentally. The problem is to mitigate the maternal immune system to tolerate the paternal haplotype of the fetus. In the case of normal pregnancy a complex series of physiological modifications can solve the problem without harmful consequences to the mother and fetus.

The outermost contact cells of trophoblasts express instead of HLA-class Ia and class II antigens non-variable HLA-C, HLA-E, HLA-F and HLA-G antigens. The first consequence of this is reduction of the activity of maternal natural killer cells and maternal dendritic cells;

Progesteron, micro-RNA and mediators influence the development of T effector-cells. The production of soluble HLA-G(5 and 6) and IL-10 supports the differentiation of Th-2 $CD4^+$ helper cells, reducing the ability of maternal cells to kill fetal cells.

Series of receptors and costimulators are expressed by the different lines of semi-allogenic trophoblast cells to bind HLA-G and mitigate maternal immune response;

The maternal immunotolerance is further facilitated by the activation of $CD4^+CD25^{bright}Foxp3^+$ regulatory T (T_{REG}) cells.

Infections have to be prevented during pregnancy. The cells of placenta express 10 Toll-like receptors a group of pattern recognition receptors responsible for innate immunity. The interferon level is also higher in the placental tissues than in the somatic fetal or maternal cells.

The complement system is also adapted to the requirements of the pregnancy and fetal damage is inhibited by the production of "assymmetric IgG antibodies" under hormonal and placental-regulation. These modifications prevent the activation of complement, cytotoxic activity, opsonising ability, antigen clearance and precipitating activity of the molecules.

The Achilles' heels of the different barriers are regularly found by virus infections. Lamina cribrosa of the blood-brain barrier, optical nerve of the eyes, etc. the risk factors of the maternal-fetal barrier has been summarised in Table 1.1.

1.1 Introduction

The different barriers of the human body are immunologically unique sites that must promote tolerance to the allogeneic external world, while maintaining host defense against possible harmful influences including pathogens. Mechanistic background of tolerogenesis is present in pregnancy, cancer, oral tolerance and anterior chamber associated immune deviation etc. It contains elements directly capable of promoting tolerogenesis such as **T regulatory (T_{REG}) cells** and inhibitory macrophages. The high content of mesenchymal and hematopoietic stem cells provides the possibility of trophic/regenerative potential, which would augment tolerogenic processes by decreasing ongoing inflammation. The application of such autologous cell sources can be used for therapeutic purposes, too. Autoimmune diseases i.e. rheumatoid arthritis can be improved on the basis of the information available (Ichim et al. 2010).

An other function of the barriers is the exchange of gases, liquids, toxic materials in order to stabilise the "*milieu enerieur*" of the body. Therefore, the barrier functions are asymmetrically bidirectional in the different surfaces of our body.

The most sofisticated unique barrier of the human being is the maternal-fetal interface, which can be considered to be a dynamic border of the infectious and non-infectious components, which have to be separated, but the allogeneic and non-infectious components have to be tolerated. The risk factors affecting the maternal-fetal barriers have been summarised in Table 1.1.

Table 1.1 Different etiologies of recurrent spontaneous abortions (Pandey et al. 2005)

Genetic, hormonal toxic	Immunology and tolerance	Microbiology
Chromosomal (Rubio et al. 2003)	Antipaternal antibodies (APCA) (Orgad et al. 1999)	Infections (Matovina et al. 2004)
Genetic (Takakuwa et al. 2003)	Autoimmune (Wramsby et al. 2000)	High fever (Czeizel et al. 2008)
Anatomical (Stray-Pedersen and Stray-Pedersen 1984)	Alloimmune factors (Eblen et al. 2000)	Prokaryonts[a]
Endocrinological (Clifford et al. 1994)	Antiidiotypic antibodies (Ab2) (Ito et al. 1999a, b)	Protozoa[a]
Placental anomalies (Lea et al. 1997)	Blocking antibodies (MLR-Bf) (Adachi et al. 2003)	Maternal-fetal infections with human viruses
Stress factors (Sugiura-Ogasawara et al. 2002)	T-1 pattern of cytokines (Lim et al. 2000)	Pelvic inflammation (Ács et al. 2008)
Smoking and alcohol (Harlap and Shiono 1980)	Natural killer (NK) cells (Faridi and Agrawal 2011)	TLR activation (Riley and Nelson 2010)
Environmental factors (Polifka and Friedman 1991)	Alteration in HLA-G expression (Aldrich et al. 2001)	

[a]Exceeding the topic of this chapter

1.1.1 Barrier of the Mucosa of Genital Organs

Lentiviruses such as HIV have a daunting challenge in gaining access to a new host predominantly through the **barriers of penile, rectal, or vaginal/cervical mucosal tissue** after sexual exposure. Multiple mechanisms have evolved to help prevent such infections, including anatomical barriers, innate inhibitors, and adaptive immune responses. For lentiviruses, it appears that in naive or even conventionally vaccinated hosts, typical adaptive immune responses are generally too little and too late to prevent infection (Keele and Estes 2011). The healthy mucous membranes The V1/V2 domain of HIV-1 gp120 mediates binding to integrin α4β7 (α4β7) on $CD4^{+}$T-cells (Arthos et al. 2008). α4β7 has been termed the gut homing integrin (Wagner et al. 1996). It is upregulated on lymphocytes in Peyer's patches and mesenteric lymph nodes, and then mediate, with chemokine receptors, the homing of these lymphocytes into gut associated lymphoid tissue (GALT) through interactions with its natural ligands, mucosal addressin cell adhesion molecule (MAdCAM) and vascular cell adhesion molecule (VCAM), which appear on the gut endothelial cells (Bargatze et al. 1995). N-linked glycosylation sites (PNGs) of V1, V2 and V4 domains of viral gp120 remain unglycosylated and surprisingly potentiate the affinity for α4β7 integrin. Therefore only a very small proportion if infecting HIV-1 (A or C subtypes) will be able to infect the mucosal lymphocytes unless an other sexually transmitted infection had not attracted and activated the CD4+ cells in the mucosa of the genital barriers (Nawaz et al. 2011).

Evidence has been presented, that antigens and cytokine signals in seminal fluid regulate the maternal immune response includes the following components: (1) the T_{REG} cell-inducing cytokine TGFβ and male alloantigens present in seminal fluid; (2) seminal fluid delivery at coitus is sufficient to induce a state of active immune tolerance to paternal alloantigen, even in the absence of conceptus tissue; (3) female dendritic cells can cross-present seminal fluid antigens to activate both $CD8^{+}$ and $CD4^{+}$ T cells, and (4) mating events deficient in either sperm or seminal plasma result in diminished $CD4^{+}$ $CD25^{+}$ $Foxp3^{+}$ T_{REG} cell populations at the time of embryo implantation. Ongoing studies indicate that the cytokine environment during priming to male seminal fluid antigens influences the phenotype of responding T cells, and impacts fetal survival in later gestation, too (Robertson et al. 2009).

1.1.2 Oral Tolerance (OT)

Oral tolerance means systemic immunological unresponsiveness to harmless antigens present in the gastrointestinal tract. The secretory IgA and IgM impair or inhibit surface colonisation of microorganisms and dampen penetration of potentially dangerous antigens. The cellular part of OT mainly depends on the development of regulatory T (T_{REG}) cells in mesenteric lymph nodes to which mucosal

dendritic cells (DCs) carry exogenous antigens and become conditioned for induction of T_{REG} cells (Brandtzaeg 2010). Tolerance to these antigens may also protect self-proteins that show immunological similarity to the intestinal normal flora. It has been suggested recently, that antigenic mimicry is one of the mechanisms contributing to the extension of OT to intestinal bacteria (bacterial homunkulus) on the basis of similar mimotopes (Kristóf et al. 2009). Cells producing **soluble HLA-G antigens** were detected in tonsils by immunohistochemistry, suggesting a role of sHLA-G in local control of T_{FH} cell chemotaxis (Morandi et al. 2010).

1.1.3 Organisation of Immune Cells

The gastrointestinal epithelium transports solutes and water between lumen and blood and at the same time forms a barrier between these compartments. This highly selective and regulated barrier permits ions, water, and nutrients to be absorbed, but normally restricts the passage of harmful molecules, bacteria, viruses and other pathogens. Inflammatory processes are accompanied by increased oxidative stress, which in turn can impair the epithelial barrier. Consequently the decrease in transcellular electrical resistance and an increase in paracellular permeability for tracers of different size can be observed (John et al. 2011).

In colonic epithelial cells, hydrogen peroxide caused tyrosine phosphorylation of occludin and dissociation of occludin and ZO-1, leading to decreased trans-epithelial resistance and increased epithelial permeability (Rao et al. 1997).

Secretory immunity is preferentially stimulated by pathogens and other particulate antigens taken up through thin "M" cells (M) located in the dome epithelium covering inductive mucosa-associated lymphoid tissue. The commensal antigens cause suppression of pro-inflammatory Th2-dependent responses (IgE antibodies), Th1-dependent delayed-type hypersensitivity (DTH), IgG antibodies, and Th17-dependent granulocytic reactions.

Intestinal immune cells are located in three **compartments**: organised gut-associated lymphoid tissue (GALT), the lamina propria, and the surface epithelium. GALT comprises Peyer's patches, the appendix, and numerous isolated lymphoid follicles. The B-cell follicles are covered by a specialised epithelium containing membrane (M) cells which, together with intraepithelial dendritic cells (DCs), transport antigens from the gut lumen into the lymphoid tissue (Neutra et al. 2001). Secretory IgA (SIgA) and secretory IgM (SIgM) are dimers and pentamers completed with the pIgR/membrane secretory component (mSC)-mediating epithelial export and rendering them resistant to digestive enzymes.

Plasma cells of B cell origin are differentiated in the *lamina propria*. In the regional lymph node plasmablasts are produced and transported into secretory glands.

In newborns, secretory IgA (SIgA) is generally undetectable in the mucosa before 10 days of age and $SIgM^+$ PCs often remain predominant up to 1 month. Elevated SIgA probably reduce the risk of allergy before the 2nd year of age,

but 70% of the participants continued breast feeding during the study (Kukkonen et al. 2010). Dendritic cells (DCs) of Peyer's patches express IL-10 mRNA in contrast to DC-s of spleen origin. Cells of mesenterial lymph nodes (MLN) and DCs are inducing α4β7 integrins enabling the homing of T-cells. IgA, with or without bound SC, but not IgG or IgM, bound selectively to murine and human M cells. Fcγμ receptor, FcαRI, and asialoglycoprotein receptor was involved in the process.

Conformational changes following antigen binding modifies the receptor binding capacity. The immune complexes can induce antigen specific immunity or immunotolerance. Beneficial effects of indigenous gut bacteria appear to be mediated largely via pattern recognition receptors (PRRs) expressed by the surface epithelium, particularly Toll-like receptors (TLRs) and similar innate sensors on the plasma membrane (apically or basolaterally) or on endosomal membranes recognise conservative microbe-associated molecular patterns (MAMPs). Polarised epithelial cells have the ability to dampen the proinflammatory effect of PRR-mediated signals coming from the luminal side. In case the microbes were able to damage the epithelial cells, PRR signalling from the basolateral side results in NF-κB activation and release of epithelial defensins to combat the infection (Brandtzaeg 2010).

Secreted immunoglobulins play an integral role in host defense at mucosal surfaces, and recent evidence shows that IgG can participate in antigen sampling from the intestinal lumen. CD23 is a type II integral membrane glycoprotein with a carboxy terminal C-type lectin head that binds its ligand, IgE, in a calcium-dependent manner. It has been shown that human IgE also could facilitate transepithelial antigen sampling. CD23 was expressed constitutively on intestinal epithelial cells (IECs), and food-allergic patients had increased levels of soluble CD23 and food-specific IgE in the stool after challenge. Specific IgE facilitated the uptake of antigen from the apical surface of an epithelial monolayer by rescuing antigen from landing into lysosomes. CD23a functions as a bidirectional transporter of IgE and can capture IgE–antigen complexes and deliver them in an immunologically intact form across the intestinal epithelial barrier (Li et al. 2006a, b).

The role of retinoic acid (RA) in the reciprocal TGF-beta-driven differentiation of T(H)17 and regulatory T_{REG} cells is important also in the control a functional immune system, in particular at the mucosal interface of the intestine (Mucida et al. 2007, 2009).

Antibacterial β defensins are protein antibiotics expressed in the oral mucosa, too (Kesting et al. 2012). Antimicrobial peptides are small, cationic, amphiphilic peptides of 12–50 amino acids with microbicidal activity against both bacteria and fungi. Mammalian defensins are composed of beta-sheet structures which are stabilised by two or three intramolecular disulfide bonds. The mammalian defensins can be subdivided into three main classes according to their structural differences: the alpha-defensins, beta-defensins and the recently described theta-defensins. Beta-defensins have been isolated from both leukocytes and epithelial cells (Schneider et al. 2005). All the genes investigated were expressed significantly more in the oral mucosa than in the skin (β-defensins 1–3 and psoriasin). Defensins were induced in the basal epitelium by bacterial extracts (Guaní-Guerra et al. 2011; Baldassarre et al. 2011).

The instruction of the immune system to be tolerant of self, thereby preventing autoimmunity, is facilitated by the education of T cells in a specialized organ, the thymus, in which self-reactive cells are either eliminated or differentiated into tolerogenic Foxp3(+) regulatory T (T_{REG}) cells. However, it is unknown whether T cells are also educated to be tolerant of foreign antigens, such as those from commensal bacteria, to prevent immunopathology such as inflammatory bowel disease. It has been shown that the **contact with commensal microbiota results in the peripheral generation of T_{REG} cells** rather than pathogenic effectors. It has been observed that colonic T_{REG} cells used T-cell antigen receptors (TCRs) different from those used by T_{REG} cells in other locations, implying an important role for local antigens in shaping the colonic T_{REG}-cell population. Many of the local antigens seemed to be derived from commensal bacteria, on the basis of the *in vitro* reactivity of common colon T_{REG} TCRs. These TCRs did not facilitate thymic T_{REG}-cell development, implying that many colonic T_{REG} cells arise instead by means of antigen-driven peripheral T_{REG}-cell development. Microbiota indigenous to the mouse colony examined was required for the generation of colonic T_{REG} cells from otherwise naive T cells. If T cells expressing these TCRs fail to undergo T_{REG}-cell development and instead become effector cells, they have the potential to induce colitis, as evidenced by adoptive transfer studies. These results suggest that the efficient peripheral generation of antigen-specific populations of T_{REG} cells in response to an individual's microbiota provides important post-thymic education of the immune system to foreign antigens, thereby providing tolerance to commensal microbiota (Lathrop et al. 2011).

1.1.4 Intranasal Inoculation and Oral Tolerance

The Achilles' heel of oral tolerance is the region of the *lamina cribrosa*. This place is a contact point between the **oral tolerance and blood-brain barrier**. Direct exchange of cells and etiological agents can be exchanged in this small region of the two large compartments.

Even stem cells may enter the CNS after intranasal administration. It may provide an extraordinary approach to overcome existing barriers of stem cell delivery for the treatment of many neurological disorders (Jiang et al. 2011a, b). Intranasal inoculation of **rabies virus** may result in 100% of mouse encephalitis within 9 days following infection, since the sensory nerves penetrating *lamina cribrosa* transported the virus directly into the brain (Lafay et al. 1991; Klopfleisch et al. 2004; Rosseels et al. 2011).

Coxsackie virus B (CVB) following dissemination, access secondary sites of infection via transmission through an endothelial monolayer such as that of the blood-brain barrier (BBB) and/or venous endothelium. Both polarized epithelial and endothelial cells function to prevent pathogen access to the interstitium, CVBs have developed strategies to subvert these barriers in order to promote their entry (Bozym et al. 2010). Coxsackievirus and adenovirus receptor (CAR) mediates

attachment by all six CVB serotypes, but is inaccessible to viruses on the luminal surface due to its localization within intercellular tight junctions. Decay accelerating factor (DAF) is a glycosylphosphatidylinositol (GPI)-anchored membrane protein. It is localized to the apical surface of polarized cells and is accessible to virus in the lumen (Shieh and Bergelson 2002).

Lipid rafts are enriched in a number of signaling molecules including receptor tyrosine kinases, the Src family of nonreceptor tyrosine kinases, small G proteins, and adenylyl cyclases (ACs) and CBA-DAF complex can easily contact lipid rafts because of the absence of cytoplasmic domain of DAF (Parton and Richards 2003). Two tyrosine kinases (Abl and Fyn) are activated by DAF clustering and both are required for CVB entry into polarized epithelial cells (Coyne and Bergelson 2006).

Human brain microvascular endothelial cells (HBMEC), represent an *in vitro* model of the **blood-brain barrier (BBB)**. CVB-induced clustering of DAF induces an immediate depletion of $Ca2_i^+$ stores. the Src family of tyrosine kinases, phospholipase C (PLC), and is mediated specifically by the IP3R isoform 3. Inositol 1,4,5-trisphosphate (IP3), the calpain family of $Ca2^+$-activated proteases plays a role in mediating the trafficking of CVB-containing vesicles within the cell. Interestingly, Ca_i2^+ release is involved in mediating CVB entry into primary human aortic endothelial cells, but is not required for CVB entry into polarized epithelial cells, suggesting that the intracellular signaling molecules hijacked by CVB to facilitate entry are distinct between the endothelium and epithelium.

The integrity of the **zona occludens** of **nasopharingheal and respiratory epithelia** may be impaired by rhinovirus and respiratory syncytial virus infections, too. The integrity of tight junctions facilitating bacterial transmigration across polarized airway epithelial cells, similar to the case with replicting rhinoviruses was found to be caused by poly(I:C), i.e. by double stranded RNA. Both stimulated Rac1 activation, reactive oxygen species (ROS) generation, and enhanced Rac1-dependent NADPH oxidase 1 (NOX1) activity, but independent of the stimulation of Toll-like receptor 3 (TLR-3). The NF-κB activation by respiratory syncytial virus (Fink et al. 2008; Yoboua et al. 2010) and IL-8 production of rhinovirus infected cells was also caused by oxidative stress (Biagioli et al. 1999). All of the above mentioned phenomena represent Achilles' heels of the gastrointestinal system. The adverse effects of the inflammatory mediators on amniotic tight junctions cause severe dysfunction of the amniotic barrier (Kobayashi et al. 2010a, b; Comstock et al. 2011).

1.1.5 The Brest Feeding

Animal experiments revealed recently, that oral feeding of mice with hydrolised whey induced the production of Fox-$P3^+$ T_{REG} cells in the mesenterial lymph nodes of the animals. The transfer of these cells into naive individuals was able to prevent the development of sensitisation and development of skin allergy passively. It is suggested, that this phenomenon is important in the prevention of development of allergic diseases (van Esch et al. 2011). The intestinal commensal bacteria possess

similar tolerising effect, too (Lathrop et al. 2011). It has been suggested earlier, that the bacterial mimotopes might play an important role in the tolerogenic effect of commensal bacteria (Kristóf et al. 2009).

In addition to contributing to passive protection, breastfeeding actively stimulates the **neonatal immune system** of the human offspring, too. Factors including lymphocytes, cytokines, hormones, lactoferrin, and anti-idiotypic antibodies are presumably involved (Corthésy 2007). The neonatal FcRn is also able for the bidirectional transport, but in contrast to rodents, immuncomplexes and not antibodies were shown to be transported from the luminal side of the gut to the dentritic cells of the mucosa for presentation (Yoshida et al. 2004).

Mother's milk also contains a number of immune cells, cytokines, and growth factors that may exert a significant biological effect in the breast-fed infant's gut, apparently enhancing in an indirect way even the subsequent health of the individual. The microbe-associated molecular patterns (MAMPs) do not only directly modulate the epithelial barrier function of neonates. Unlike intestinal macrophages, intestinal epithelial cells (IECs) acquire TLR tolerance immediately after birth by exposure to exogenous endotoxin to facilitate microbial colonization and the development of a stable intestinal host–microbe homeostasis (Lotz et al. 2006). Intestinal colonisation of lactobacilli and bifidobacteria is promoted by breast milk because it acts as prebiotics through its large amounts of oligosaccharides (Brandtzaeg 2010). *E. coli* is a strong inducer of IL-10 secretion being crucial for maintained expression of the Foxp3 transcription factor of T_{REG} cells (Murai et al. 2009).

Intranasal dry powder measles vaccination was also successful (Lin et al. 2011). The virus obviously was dissolved on the surface of cells with $CD46^+$ receptors on the surface of the bronchial mucosa. The transfer of viruses is one of the Achilles' heels of the OT.

1.2 The Blood-Brain Barrier (BBB)

The blood-brain barrier (BBB), comprised of the endothelial cells lining the cerebral vasculature, regulates the paracellular and transcellular passage of molecules and solutes between the cerebral vessels and the brain neuropils. The site of barrier function is at the level of the endothelium, astrocytes are known to induce and maintain permeability properties of the BBB. Another potential role of astrocytes is in the actual regulation of water transport across the BBB, mainly because of the highly polarized localization of **aquaporin-4 (AQP4)** in the perivascular endfeet of astrocytes (Quick and Cipolla 2005). During the telencephalon morphogenesis the immature astroglia cells play a role in the early establishment of the distribution pattern of the neural microvessels and in their growth and maturation. Astrocytes are well known to establish close anatomical and functional relationships with the adult brain microvessels and to induce the expression and maintenance of the blood-brain barrier (BBB) phenotype of the brain endothelial cells (Virgintino et al. 1998). One pathologic condition that may involve AQP4 and edema formation is

eclampsia. Eclampsia is a serious complication of pregnancy due to its neurological complications, including headaches, nausea, vomiting, and seizures (Mas and Lamy 1998). Eclampsia seems to be similar to hypertensive encephalopathy in which an acute rise in blood pressure causes forced dilation of the cerebral arteries and arterioles, decreased cerebrovascular resistance, and increased pressure on the microcirculation, resulting in disruption of the BBB and vasogenic edema (Engelter et al. 2000).

Pregnancy has been shown to up-regulate aquaporin expression in other organs such as the uterus. Rat experiments suggested that pregnancy and the postpartum state upregulated AQP4 protein located around the intraparenchymal blood vessels, a consequence that could promote edema formation when blood pressure is acutely and excessively elevated, as during eclampsia (Quick and Cipolla 2005).

Some enterovirus 71 (EV71) antigens were shown to induce cross-reactivity to human cerebra. The infection led to a persistent viremia and a transient increase in BBB permeability, but only low levels of virus could be detected in the mice brain. The brain binding partner of EV71 induced IgG was not identified. The increase of BBB permeability after EV71 infection could result in the entrance and localization of the IgG into brain tissues. The increase of BBB permeability in neonatal mice under EV71 infection and the entry of brain cross-reactive IgG were supposed to play a role in the development of subsequent clinical symptoms (Jia et al. 2010).

Transcellular migration of neutrophil granulocytes forms an additional Achilles' heel of the blood-brain barrier, since both cells and bacteria were shown to penetrate the plexus chorioideus capillary vessels and epithelium in the presence of intact *zona occludens* (Wewer et al. 2011).

In utero the blood-brain barrier (BBB) is not yet developed, therefore the transplacental antibodies are able to react with fetal neurones, too. The newborns of mothers suffering from SLE may have learning and memory disturbances (Cohen-Solal and Diamond 2011).

1.3 The Human Skin Is Homing More T-Cells Than the Blood and Lymphoid Organs

1.3.1 T Cells from Normal Human Skin

T cells from normal human skin using both established and novel methods were tested. Skin resident T cells expressed high levels of cutaneous lymphocyte antigen positive (CLA^+), CCR4, and CCR6, and a subset expressed CCR8 and CXCR6 chemokine receptors. Skin T cells had a remarkably diverse TCR repertoire and were mostly Th1 memory effector cells with smaller subsets of central memory, Th2, and functional T regulatory cells (Clark et al. 2006a, b).

Exposure to parasites in the skin coincides closely with vaccine failure. Malaria naïve subjects, (which excludes bloodstage immunosuppressive effects) live-parasite immunization transiting unmodified skin is inefficient. Immunity diminishes after unmodified skin-parasite interactions and is significantly less robust generated via skin exposure (Guilbride et al. 2010). Subcutaneous antigen delivery bypasses plenty of T_{REG} cells present within the cutis. This is the reason, why mosquito bites result in tolerance (i.e. impairment of immune response, but mitigation of the clinical symptoms in children).

The presence of protein antibiotics (β defensin 1–4) were identified in the human skin, too (Ali et al. 2001).

Proteoglycane recognition proteins 1–4 are coded for by the genes *Pglyrp 1–4*. Their products are recognising bacterial peptidoglycans, and function in antibacterial immunity. These can protect mice against experimental colitis, and arthritis (Saha et al. 2009, 2010) and are able to modulate the development of experimental atopic dermatitis. It has been shown, that Pglyrp3 and Pglyrp4 products limit over-activation of Th17 cells by promoting accumulation of T_{REG} cells at the site of chronic inflammation, which protects the skin from exaggerated inflammatory response to cell activators and allergens. By contrast, Pglyrp1 protein has an opposite pro-inflammatory effect in the skin (Park et al. 2011).

1.3.2 Dendritic Cells, Skin and Mucosal Barriers

Langerhans cells have been discovered in 1868 (Langerhans 1868). Three fractions of DCs in the human peripheral blood using a panel of mAbs have been characterised. One of them has the capacity to become LCs. Blood DC fractions (subsets) are different not only in their maturational stages, but also in their lineage or differentiation pathways (Ito et al. 1999a, b). Langerhans-like cells have been identified already among salmonid lymphoid cells (Lovy et al. 2011). LCs as scattered starry cells in the basal and supra-basal of epidermis layers. In the subcutaneous lymph-nodes, LCs could be demonstrated already from the 4th month of foetal life. LCs were suggested to be of neural crest origin, similar to the melanocytes (Muretto 2008). Langerhans cells utilize CD1a and langerin to efficiently present nonpeptide antigens to T cells (Hunger et al. 2004).

Dendritic cell (DC) subsets in mucosal tissues are thought to transmit HIV-1 to T cells through C-type lectins. In mucosal tissues, DC subsets can be distinguished by their expression of C-type lectins. HIV can interact concomitantly with non-LC dendritic cells in two separate and distinct ways: a *CD4*- and *CCR5*-dependent infection pathway and a *CD4*- and *CCR5*-independent capture pathway mediated by DC-SIGN, a C-type lectin molecule. Langerhans cells (LCs) specifically express Langerin and DCs express DC-SIGN (de Witte et al. 2007).

LCs reside in the epidermis of the skin and in most mucosal epithelia, such as the ectocervix, vagina and foreskin, whereas DC-SIGN$^+$ DCs reside in the subepithelium

(Veazey et al. 2005; Veazey and Lackner 2005). Thus, LCs are the first DC subset to encounter HIV-1 (Kawamura et al. 2005). LCs are resistant to this subversion and do not efficiently transmit virus to T cells, unless a C-type lectin is inhibited by a C-type lectin inhibitor mannane (de Witte et al. 2007).

Langerin (CD207) is a C-type lectin expressed in human exclusively by Langerhans cells (LCs). Langerin is a type II transmembrane protein that contains one calciumdependent carbohydrate recognition domain with a short cytoplasmic tail with a proline rich motif. Langerin forms a trimer on the cell surface and upon crosslinking with either a cell-bound or a soluble ligand. Langerin is inducing the formation of Birbeck granules: Organelles, consisting of pentalamellar and zippered membranes that can be visualized using electron microscopy. The Birbeck organelles have only been found in LCs. The function of Birbeck granules is not known yet (Geijtenbeek et al. 2000; de Witte et al. 2008).

Human primary LCs were shown to be capable of capturing measles virus (MV) through the C-type lectin Langerin. Both immature and mature LCs presented MV-derived antigens in the context of HLA class II to MV-specific $CD4^+$ T cells. Immature LCs were not susceptible to productive infection by MV and did not present endogenous viral antigens in the context of HLA class I. In contrast, mature LCs could be infected by MV and presented de novo synthesized viral antigens to MV-specific $CD8^+$ T cells. Immune activation of LCs seems a prerequisite for MV infection of LCs and subsequent $CD8^+$ T-cell priming via the endogenous antigen presentation pathway (de Jong and Geijtenbeek 2010; van der Vlist et al. 2011).

Direct or competitive inhibition of Langerin function and inhibition of the Langerint expression was shown to facilitate HIV-1 replication in LCs (de Jong and Geijtenbeek 2010). The inhibition of Toll like receptors had no influence on the restricting function of Langerin i.e. HIV replication in dendritic cells (Ogawa et al. 2009).

Complement also can influence the adaptive immune response by modulating DC function and thus regulating antigen specific T cell responses. C1q was shown to activate dendritic cells (Götherström et al. 2005; Csomor et al. 2007; Fazekasova et al. 2009). Murine bone marrow dendritic cells (BMDCs) are important local source of complement and can react to activated complement products (C3a, C5a) through specific receptors (C3aR, C5aR) expressed on DCs, which leads to cell activation and functional modulation.

Monocyte derived $CD1a^+CD14^-$, dermal $CD1a^+$DC-$SIGN^+$, Langerhans $CD1a^+$ $Langerin^+$, myeloid $CD1c^+CD19^-$, plamacytoid $CD45RA^+CD123^+$ express many of the components of the classical and alternative and terminal pathways of complement.

Human DCs have receptors C3aR and C5aR known to recognise the biologically active peptides C3a and C5a. Membrane receptor proteins inducing immune adhesion CR3, CR4 CRIg and bind C3b and metabolites iC3b and C3d. The human DC surface is characterised by membrane bound regulators of complement activation, which are also known to participate in intracellular signalling (CD46, CD55, CD59). These findings suggest, that the complement system can influence both the antigen presentation and autoimmune illnesses (Li et al. 2011) in addition to the many other circumstances discussed above.

1.4 The Blood-Retinal Barrier and Sympathetic Ophtalmia

Interstitial retinoidbinding proteins, are capable of eliciting uveitis. Another recent histochemical investigation suggests that sympathetic ophtalmia (SO) is mediated by delayed T-cell hypersensitivity directed at surface membrane antigens shared by photoreceptors, retinal pigment epithelial cells, and choroidal melanocytes (Chaithanyaa et al. 2011). The eye which has suffered penetrating injury, has to be enucleated within 2 weeks in order to prevent sensitisation. The absence of lymphatics within the eye may play an important role in the pathogenesis of SO. Intraocular antigens circulate to the blood and spleen following penetrating injury, bypassing local lymph nodes, which may result in the induction of blocking antibodies or suppressor cells in spleen. Bacterial or other microbial contamination may potentiate sensitisation (Chaithanyaa et al. 2011).

The barrier can be penetrated by therapeutic methotrexate, methylpredenisolone, mycophenolate mofetil, cyclosporine and infliximab. The therapy using anti-tumor necrosis factor (anti-TNFα), but not daclizumab (monoclonal antibody specific for the receptor of interleukin 2) therefore only the first group can achieve prolonged remission of the patient (Gupta et al. 2011).

This disease indicates, that the fetal thymus and immune system did not met these antigens during the embryonic development. The transbarrier metabolism, however, was found to be very active. In diabetic retinopathy 27 cytokines and chemokines were found in the vitreous fluid. The development of both central retinal vein occlusion and rethinopathy seemed to be associated with increased concentrations of inflammatory cytokines IL-10, IL-13, platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). The screening was performed using a microbead-array system by the authors (Suzuki et al. 2011).

Expression and organization of a well-developed tight junction (TJ) complex in the inner retinal capillaries contributes to the formation of the internal blood-retinal barrier (iBRB). Transport of molecules across the vascular endothelium may occur by transcellular pathways, including specific transporters or by paracellular transport, which includes transport across the junctional complex, across a broken junctional complex, or across a large gap caused by cell death or cell division. Oncotic pressure and hydrostatic pressure drive both fluid and solute transport.

A **three-pore model** of transport – namely, transcellular transport through vesicles, broken TJs, and large pores, also termed leaky junctions have been developed. Bovine retinal endothelial cell (BREC) monolayer was used for the tests seeded onto a TUNEL assay kit. The fluorescent solutes were carboxytetramethylrhodamine (TAMRA of a Stokes diameter of 1.3 nm), 70-kDa TRITC-dextran (of 11 nm) and low density lipoproteid (Dil-LDL of 22 nm). The results support the existence of an indirect pathway by which iBRB permeability is increased through the upregulation of retinal VEGF in response to hyperglycemia (Lopez-Quintero et al. 2011).

Examinations using human "Angiogenesis Antibody Array" for retinal pigment endothelial (RPE) cells showed high production of interleukin-8 (IL-8) and

monocyte chemotactic protein-I (MCP-I). Stimulation of RPE cells (mediated by Toll-like receptor 3) with the dsRNA analogue poly(I:C) enhanced the secretion of IL-8 and MCP-I, as well as the expression of junctional adhesion molecule-I (Jam-I) and intracellular adhesion molecule-I (ICAM-I), and promoted the adhesion of monocytes to these cells. In contrast, stimulation with the CpG-DNA motif (mediated by Toll-like receptor) only enhanced the secretion of IL-8 and enhanced phagocytosis in RPE cells. These results may indicate that TLR 3 and 9 play a distinct role in the inflammatory response that clears viruses from the retina (Ebihara et al. 2007).

1.4.1 Virus Infections of the Eye Bulb, Lens and Retinal Epithelium

Rubellavirus and human hervesvirus 2 (HHSV-2) were identified in the lens aspirate of newborns suffering from connatal cataract (Shyamala et al. 2008). **Herpes simplex virus 1 and varicella-zoster virus encephalitides** were followed by acute retinal necrosis after some delay. The delay, however may last sometimes for decates (Klein and Lefebvre 2007; Vandercam et al. 2008). The way of HSV-1 to retinal cell layers were mediated by nectin-1 receptor being the major determinant of HHSV-1 entry into retinal pigment epithelial (RPE) cells. In addition, nectin-1 can influence cell to-cell spread of the virions involving membrane fusion. This is probably the mechanism helping the virus to enter the inner eye (Tiwari et al. 2008). **Human cytomegalovirus (HCMV)** produced in epithelial cells preferentially fuses with the plasma membrane of retinal pigmented epithelial cells, whereas fibroblast-derived virus mostly enters by receptor-mediated endocytosis (Wang et al. 2007). Human cytomegalovirus retinitis of patients suffering from HIV-1 disease occurs frequently, too (Geng et al. 2011). Eyes of **AIDS patients** with a clinical history of HCMV retinitis were tested positive for HCMV, but also for **JC papillomavirus and HIV-1 provirus** (Eberwein et al. 2005). Multifocal choroiditis is the most common ocular manifestation associated **with West-Nile Virus (WNV)** infection, with a typically benign clinical course. Less frequent ocular lesions, including optic neuritis and occlusive vasculitis, frequently induce persistent and likely permanent visual deficit (Chan et al. 2006).

1.4.2 The Effect of Pregnancy and Diabetes on the Blood-Retinal Barrier

Normal pregnancy was characterized by an activation of circulating leukocytes as part of a generalized immune response. This leukocyte activation is marked by upregulation in the expression of different adhesion molecules such as CD11a,b/CD18, CD54 (ICAM-1) and CD49d as well as integrins and selectins present on the surface

Table 1.2 Cytokine changes during pregnancy and possible influence on retinopathy (Kaštelan et al. 2010)

TNF-α	Increased mediator of endothelial dysfunction in preeclampsia
IL-1α	Increased in serum
IL-1β	No change in serum concentration but elevated vitreous level
IL-4	Reduced in serum
IL-6	Increased serum and vitreous levels; pro-inflammatory cytokines breakdown of blood-retinal barrier and mediator of endothelial dysfunction in preeclampsia, highest level at labour;
IL-8	Angiogenic and fibrovascular proliferative effect (ocular neovascularisation)
sIL-2R	Increased vitreous concentration
IL-10	Increased in serum
VEGF	Increased in serum
EGF	Increased in serum
ICAM-1	Increased on the membrane of endothelial cells; Increased leukocyte adhesion;
VCAM-1	Increased on the membrane of endothelial cells; Increased leukocyte adhesion;
E-selectin	Increased on the membrane of leukocytes; Increased leukocyte adhesion; Occl.
P-selectin	Increased on the membrane of leukocytes; Increased leukocyte adhesion; Occl.

PDR proliferative diabetic retinopathy, *TNF* tumor necrosis factor, *IL* interleukin, *VEGF* vascular endothelial growth factor, *EGF* epidermal growth factor, *ICAM* intercellular adhesion molecule, *VCAM* vascular cell adhesion molecule, *Occl* capillary occlusion

of circulating leukocytes. These activated leukocytes have the increased potential to bind to the endothelium of blood vessels via interactions with ICAM-1 and VCAM-1 molecules. One of the essential pathologic events in the development of diabetic retinopathy is activated during pregnancy and could therefore be at least partially responsible for its progression in the gestation period. Patients suffering form proliferative diabetic retinopathy (PDR) possessed increased vitreous concentrations of interleukin-1beta (IL-1beta), IL-6, soluble IL-2 receptor (sIL-2R) and IL-8 were found. Their sera contained elevated levels of tumor necrosis factor-alpha (TNF-alpha), IL-6, IL-8 and sIL-2R (Kaštelan et al. 2010). The cytokine changes during pregnancy and possible influence on retinopathy are summarised in Table 1.2.

Preeclampsia is a well recognized risk factor for the progression and deterioration of diabetic retinopathy during pregnancy. It is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction as part of a general inflammatory reaction. Analysis of PCT and IL-6 concentrations in serum allows to identify women that are more likely to deliver newborns with symptoms of severe infection. In cases of severe infection, the usefulness of procalcitonin (PCT) measurement surpasses any currently used methods (Camacho et al. 2010).

1.5 Blood Testicle Barrier (BTB)

The assymmetric nature of the blood-testicle barrier has been discovered first (Berencsi and Kereszti 1976), when Scarlet Red and p-Dimethylamino-azobenzene dissolved in paraffin oil has been injected into rabbit testicles. p-Dimethylamino-azobenzene

caused no significant changes in the macromolecular fractions of the blood, while scarlet Red injected into the testicles caused a significant increase of the total lipids in the second week after the exposition. Similar effect could not be observed when Scarlet Red was introduced by any other route.

The difference in the protein content of human seminiferous fluid and blood was detected first by Koskimies et al. (1973) detecting the existence of a barrier.

Very different immunological environments are represented by the testis, where sperm develop, and by the epididymis, where sperm mature and are stored. In comparison with the elaborate blood-testis barrier, the tight junctions of the epididymis are much less effective. Unlike the seminiferous epithelium, immune cells are commonly observed within the epithelium, and may even be found within the lumen, of the epididymis (Le Tortorec and Dejucq-Rainsford 2010; Hedger 2011). The function of the blood-testis barrier formed by Sertoli cells protects autoimmunogenic haploid germ cells from the attack by the autoimmune system. In mice infertility was caused by induction of experimental autoimmune orchitis (EAO) and by the surgical placement of testes, epididymides and vasa deferentia (TEV) into the abdominal cavity or subcutaneous space from a syngeneic donor (Terayama et al. 2011).

Traumatic spinal cord injury (SCI) was shown to impair tight junctional integrity within the seminiferous epithelium. Three days after post-SCI, decreased expression of the tight junction protein occludin was observed. High expression of the proinflammatory cytokine interleukin-1 beta was detected indicating inflammation. $CD68^+$ immune cell infiltrate and mast cells were also detected within the seminiferous epithelium of both acute and chronic SCI groups but not in controls. The integrity of the BTB was measured by gadopentate dimeglumine (Gd) injected intravenously. The results indicate that the BTB remains compromised and testis immune cell infiltration persists for months after the initial injury (Dulin et al. 2011).

Drug transporters i.e. efflux pumps such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are localized at the blood-testis barrier (BTB), where they protect the testis from drugs and xenobiotics that are detrimental to spermatogenesis. At the same time, efflux pumps might also preclude entry of non-hormonal contraceptives to the testis. In more recent studies, P-gp function was correlated with BTB integrity as summarised in a recent review (Mruk et al. 2011).

Virus infection of testicles. HCMV was detected in male germ cells, both in sperm samples and in testis organotypic culture. The virus may infect immature germ cells which develop to mature **HCMV**-carrying spermatozoa. A considerable decrease in the number of immature germ cells indicates that HCMV produces a direct gametotoxic effect and can contribute to male infertility (Naumenko et al. 2011).

Endogeneous retrovirus 9 (HERV-9) was found to carry the *TP63* locus only recently in evolution and is unique to humans and great apes (Hominidae). A corresponding p63 protein is the sole p63 species in healthy human testis, and is strongly expressed in spermatogenic precursors but not in mature spermatozoa (Beyer et al. 2011).

Extremely seldom the **West Nile virus (WNV)** was found to replicate in endotelial cells of teticles (Armah et al. 2007). Both testicle and epididimal cells were found to be susceptible to **HIV-1** (Roulet et al. 2006).

Orchitic **SARS** testes displayed widespread germ cell destruction, few or no spermatozoon in the seminiferous tubule, thickened basement membrane, and leukocyte infiltration. The numbers of $CD3^+$ T lymphocytes and $CD68^+$ macrophages increased significantly in the interstitial tissue compared with the control group ($P < 0.05$). Severe acute respiratory syndrome (SARS) viral genomic sequences were not detected in the cells. The inflammation was the result of a possible immune response (Xu et al. 2006). **Papillomaviruses** were shown to replicate in both Leydig cells and Sertoli cells of human testicles (Martorell et al. 2005). **Mumps Paramyxovirus** attacks the testicular glands, leading to parenchymal inflammation, separation of seminiferous tubules and perivascular interstitial lymphocyte infiltration. This infection was the most frequent cause of orchitis sometimes resulting sterility before the introduction of vaccination (Masarani et al. 2006). Mumps virus was isolated from the semen 14 days after onset of parotitis and mumps RNA was detected in semen for up to 40 days using RT-PCR (Jalal et al. 2004).

1.6 Unique Features of the Maternal-Fetal Barrier

Maternal-fetal barrier represents an initial contact point for genital pathogens and, therefore, has specialized innate and adaptive immune attributes. This same tissue, however, must simultaneously tolerate the growing pregnancy, allowing allogenic fetally derived placental cells to reside in direct apposition with immunocompetent maternal lymphocytes. $CD56^{bright}CD16^{dim}$ natural killer (NK)-like cells (decidual NK cells) and $CD3^+$ T cells comprise the two major subsets of decidual lymphocytes. The fetomaternal barrier has to be capable to prevent penetration of harmful substances and infectious agents, but in the same time without injuries caused to the semiallogenic fetal tissues. This dynamic role is fulfilled by many different functions and mechanisms. The clonal deletion mechanism of B-cell tolerance has been shown first in mice (Nossal and Pike 1975).

Peptide antibiotics are present in the vernix caseosa and in the skin of the healthy newborn infant, indicating effective innate immune protection already during fetal and neonatal life (Marchini et al. 2002). Beta-defensins have been isolated from both leukocytes and epithelial cells (Schneider et al. 2005). Human antimicrobial proteins, β-defensins are also expressed at the human chorioamniotic barrier (Polettini et al. 2011).

In chorioamnionitis, intra-amniotic infections render the amniotic fluid an adverse environment for the foetus and increase the risk of foetal mortality and morbidity. It is still **unclear how infection crosses the amniotic barrier, which is made up of tight junctions (TJs).** Amniotic TJs were disrupted by single applications of interleukin (IL)-1β, IL-6, tumour necrosis factor-α (TNF-α) and prostaglandin E2.

In organ cultures of amniotic membrane these inflammatory mediators decreased the claudin-3 and claudin-4 levels at the apical junction at different times. Artificial injection of IL-6 into the amniotic cavity concurrently induced the disruption of amniotic TJs by decreasing the claudin-3 and claudin-4 levels at the apical junction resulting in the dysfunction of the amniotic barrier. The injection of TNF-α weakened the amniotic barrier by inducing apoptosis of the amniotic epithelial cells, with no decrease in claudin-3 and claudin-4 at the apical junction. The administration of the amniotic fluid of pregnant mice with bacterial lipopolysaccharide caused dysfunction of the amniotic barrier and disruption of TJs, involving the decrease of claudin-3 and claudin-4 levels at the apical junction and apoptosis in the amniotic epithelium (Kobayashi et al. 2010a, b).

1.7 Immunomodulation of the Maternal Immune System in Order to Tolerate Fetal Tissues

In humans placental trophoblast cells encounter the maternal immune system in two main areas – the villous trophoblast cells interact with the maternal blood and the **extravillous trophoblast** cells interact with the uterine tissue. In humans, the **syncytiotrophoblast** is therefore in contact with the systemic but not the uterine immune components of the mother. The syncytiotrophoblast expresses no MHC antigens on its surface, which is consistent with the concept that the placenta is immunologically neutral. Indeed, it has been difficult to demonstrate any systemic maternal T- or B-cell responses to trophoblast cells (as opposed to fetal cells that cross into the maternal circulation) during human pregnancy. The outermost layer of the human placenta is devoid of classical class I human leukocyte antigens (HLA-A, HLA-B, and HLA-C) and class II proteins (HLA-DR, HLA-DQ, and HLA-DP). Although this prevents recognition by maternal T lymphocytes, the lack of class I molecules leaves these cells susceptible to attack by natural killer (NK) cells. HLA-C is the only HLA molecule expressed by trophoblast cells that shows any appreciable polymorphism.

There are qualitative differences in all systemic T- and B-cell responses in pregnancy because of the altered clinical course of autoimmune diseases and viral infections during pregnancy. For example, the symptoms of rheumatoid arthritis (which is TH1-cell mediated) improve during pregnancy, whereas those of systemic lupus erythematosus (which is T_H2-cell mediated) worsen and this is presumably caused by the bias away from TH1-towards TH2-cell responses.

The second area of contact is between invasive extravillous trophoblast (EVT) cells and immune cells in the decidua. In contrast to the syncytiotrophoblast, extravillous trophoblast cells express an unusual combination of **HLA-C, HLA-G, HLA-E** and **HLA-F** molecules (Shobu et al. 2006). Extravillous trophoblast cells have an extraordinarily **high proliferating capacity** and their telomerase activity is substantially higher than that of somatic cells. Survivin, a protein that promotes proliferation and inhibits apoptosis, is overexpressed in trophoblast cells.

Insulin-like growth factor (IGF) stimulates proliferation of trophoblast cells through the MAPK pathway and survival via activation of the PI3K pathway by binding to its receptor IGF1R. The fetal form of insulin receptor itself (IRA) reacts also with insulin-like growth factor 2 (IGF-2) participating in the regulation of trophoblast proliferation. In contrast to cancer cells trophoblasts follow an organized pattern of differentiation from proliferation to invasion without distant metastasis (Marco et al. 2009). To promote invasion the epithelial trophoblasts differentiate and mesenchymal transition occurs, which results in loss of cell-to-cell contact inhibition and the loss of cell polarity. Cells secrete proteases required for the spread in the decidua. The expressed HSP27 is corresponding to the matrix protease MMP-2 (Soundararajan and Rao 2004; Holtan et al. 2009, 2011; Ma et al. 2010).

Trophoblast cells, however, directly in contact with the maternal tissues express the class I molecule **HLA-G**, which may be involved in **protecting the trophoblast from recognition by NK cells**. HLA-G is sufficient to protect otherwise susceptible target cells from lysis by activated NK1 and NK2 cell lines and clones that are specific for distinct groups of HLA-C alleles. HLA-E, -F, and -G, have restricted expression, few variants, and appear rarely to be immunostimulatory (Carosella et al. 2003). One class Ia **antigen**, HLA-C, and the three class Ib **antigens** are differentially expressed by **trophoblast** cell subpopulations. HLA-G5 and HLA-G6 are the soluble isoforms of the antigen (Sargent et al. 2006). HLA-G5 is a homodimer without β2-microglobulin (β2m). The results suggest that the β2m-free structure has selective functional advantages for trophoblast cells, perhaps in evading immune recognition (Apps et al. 2007; Kuroki and Maenaka 2007; Morales et al. 2007). The cell migration from the fetus to the mother is a well known phenomenon during pregnancy (Dawe et al. 2007). It is hypothesised, that the HLA-G allels on the surface of the fetal cells might play a role in the long term survival of microchimeric cells in the maternal organisms.

A systematic sequencing study of *HLA-G* alleles was done obtaining the complete genomic sequence of **16 different *HLA-G alleles***: nine alleles were intron and exon confirmatory sequences, four were exon confirmatory and new intron described sequences, and three were new alleles Human leukocyte antigen-G allele polymorphisms have evolved following three different evolutionary lineages based on the alterations of intron sequences (Cervera et al. 2010, 2011). In Brasil 28 different *HLA-G haplotypes* were identified (Castelli et al. 2011). HLA-G polymorphisms may be associated with HPV infection and **squamous intraepithelial lesions (SIL)**, consequently representing a profile of predisposition to cervical cancer and miscarriage (Moreau et al. 2008; Simões et al. 2009).

It has been suggested recently, that **HLA-G is expressed also by stem cells other than hematopoetic origin** (Selmani et al. 2008, 2009). The panleukocyte marker CD45 is missing from the mesenchymal stem cells (MSC). HLA class I antigens were found to be expressed, but only to a low level in MSC. HLA class II antigens were not expressed at all. (Castelli et al. 2009). MSCs, through HLA-G5, affect innate immunity by inhibiting both NK cell-mediated cytolysis and interferon-γ secretion (Selmani et al. 2008).

The regulation of HLA-G expression. Progesterone was shown to play role in uterine homing of NK cells and in upregulating HLA-G gene expression. At high concentrations, progesterone is a potent inducer of Th2-type cytokines as well as of leukemia inhibitory factor (LIF) and macrophage-colony stimulating factor (M-CSF) production by T cells. A protein called progesterone-induced blocking factor (PIBF) have been cloned (Polgár et al. 2003). PIBF an inducer of Th2-dominant cytokine production mediates the immunological effects of progesterone. PIBF binds to a novel type of the IL-4 receptor and signals via the Jak/STAT pathway, to induce a number of genes, that not only affect the immune response, but might also play a role in trophoblast invasiveness (Szekeres-Bartho et al. 2009).

Soluble HLA-Gs (sHLA-G) was shown to mitigate the maternal immune response directed to the fetus by **downregulating expression** of CCR2, CXCR3 and CXCR5 in $CD4^+$ T cells; CXCR3 in $CD8^+$ T cells; CXCR3 in Th1 clones; CXCR3 in TCR Vd2c9 T cells, **but upregulated CXCR4 expression** in TCR Vd2c9 T cells. sHLA-G **inhibited *in vitro* chemotaxis** of $CD4^+$ T cells towards CCL2, CCL8, XCL10 and CXCL11; CD8+ T cells towards CXCL10 and CXCL11; Th1 clones towards CXCL10; and TCR Vd2c9 T cells towards CXCL10 and CXCL11. **Phosphorylation** of Stat5, p70 s6k, β-arrestin and SHP2 **was also modulated** by sHLA-G treatment (Morandi et al. 2010).

It has been reported that **microRNAs (miRNA)** may have allele-specific targeting for the 3′ untranslated region (3′ UTR) of the HLA-G locus. On the basis of an *in silico* analysis it was supposed, that several miRNAs might have also role in the regulation of HLA-G expression (Castelli et al. 2009, 2010). In a tissue culture system the overexpression of miR-152 reduced the expression of HLA-G therefore the cells of cytotrophoblast origin became less resistant to NK-cell lysis (Zhu et al. 2010). The ras-responsive element 1 (RREB-1) was shown to bind to the promoter of ***HLA-G*** being probably a repressor of the gene. Human cytomegalovirus (HCMV)-carrier cells and HIV-1 infection can derepress the HLA-G expression (Flajollet et al. 2009; Moreau et al. 2009; Donadi et al. 2011). HLA G1-G2, and G5-7 allels are expressed in myeloid and plasmacytoid dendritic cells present in the cord-blood circulation (Román et al. 2009). Human leukocyte antigen (HLA)-G has direct inhibitory effects on natural killer cells (NK), dendritic cells (DC), T cells and can induce tolerant regulatory cells. The expression of HLA-G has been correlated with the tolerance of the fetus, the acceptance of organ transplants, and the immune escape of tumor cells of virus-infected cells.

Aberrant and/or **virus infection dependent induction of HLA-G** expression has been postulated as one of the initiating steps in the development of malignancies. The plasma concentration of soluble HLA-G can be used as surrogate marker for certain viruses (Yan 2011), for hepatitis B virus (HBV) infection (Shi et al. 2011), HCV infection (Weng et al. 2011). The induction of HLA-G by Epstein-Barr virus (EBV) was found to be dependent also on the culture conditions of the cells (Gazit et al. 2007). The mechanism of the release of the soluble plasma HLA-G protein was clarified in the case of HCMV, since the virus-coded US-10 protein facilitated the release of the HLA-G antigen from the membranes of infected cells (Zheng et al. 2009; Park et al. 2010).

The 14 bp insertion/deletion "indel" haplotype polymorphism of HLA-G-3 was suggested to be a marker for genetic susceptibility to hepatocellular carcinoma (HCC) in Chinese populations (Jiang et al. 2011a, b). The HLA-G 14 bp insertion/deletion polymorphism is a putative susceptibility factor also for active human cytomegalovirus infection in children (Weng et al. 2009).

Cell surface HLA-G expression was markedly induced in influenza A/H1N1v-infected and seasonal influenza A/H1N1-infected patients, and increased T_{REG} count was observed only in A/H1N1v-infected patients. Given its immune-suppressive property, elevated cell surface HLA-G expression may help to explain the virus escaping from host immune control (LeBouder et al. 2009; Chen et al. 2011). Chronic hepatitis B virus infection was also stimulating HLA-G synthesis (Souto et al. 2011). Rabies virus avoids inducing neuronal cell death, but also 'protective' T cells that migrate into the infected nervous system are killed by apoptosis or inactivated, as a result of the overexpression of immunosubversive molecules such as FasL, HLA-E, HLA-G and B7-H1 (Mégret et al. 2007; Lafon 2008).

Especially in Epstein-Barr virus (EBV)-negative **classical Hodgkin's lymphoma (cHL)**, the neoplastic Hodgkin-Reed-Sternberg (HRS) cells have lost protein expression of major histocompatibility complex (MHC) class I, enabling escape from cytotoxic T lymphocyte (CTL) responses. Induction of HLA-G protein expression in HRS cells contributes to the modulation of immune responses observed in **classical Hodgkin's lymphoma** (Diepstra et al. 2008). Membrane linked HLA-G molecules were expressed in a significant number of benign and premalignant oral lesions, but it was not correlated with human papillomavirus (HPV) infection or oral cancer (Fregonezi et al. 2010).

The soluble HLA-G5 and G6 drive **transforming growth factor-β1 (TGF-β1)** production of myelomonocytic cells. High doses of both significantly decreased interleukin (IL)-10 and dramatically increased **TGF-β1 production**. Differential effectiveness between the isoforms was demonstrated in dose-response studies, as was differential binding to inhibitory immunoglobulin-like transcript (ILT) receptors for HLA-G, ILT2 and ILT4.ILT2 and ILT4 in receptor-blocking studies.

How are adverse maternal T-cell responses to paternally expressed HLA-C molecules or other unidentified trophoblast-cell antigens avoided?

Each cell type express a specific surface receptor for human leukocyte antigen (HLA)-G (an MHC class Ib protein that is expressed on extravillous trophoblasts), LILRB1 on $CD14^+$ macrophages and KIR2DL4 on $CD56^+$NK cells (Li et al. 2009).

Another possible mechanism to explain the lack of uterine T-cell activation in normal pregnancies depends on the high-avidity binding of HLA-G **to leukocyte immunoglobulin-like receptors (LILRs)** expressed by myelomonocytic cells. Increased expression of LILRB1 is associated with the induction of a 'tolerogenic' population of DCs, which, in a transplantation setting, results in tolerance. HLA-G-induced tolerance was due to decreased MHC class II peptide presentation by the tolerogenic DCs. Unlike blood NK cells, all uterine NK cells express high levels of the C-type lectin family member CD94–NKG2A, which binds to HLA-E resulting in inhibition of NK-cell cytotoxicity (Lopez-Botet et al. 2000).

The receptors on NK cells that recognize HLA-G have been also identified (Pazmany et al. 1996; Bainbridge et al. 2000a, b). Decidual natural killer (NK) cells play key developmental roles at the feto-maternal interface. Individual differences in NK-cell interactions are dependent on the combinations of variable killer immunoglobulin-like receptor (KIR) and HLA class-I gene products (Faridi and Agrawal 2011). A physiologic condition associated with a shift in NK homeostasis toward a noncytolytic phenotype is normal human pregnancy, where expansion of weakly cytotoxic $CD56^{bright}CD16^{dim/-}$ NK cells occurs. $CD56^{bright}$ NK cells may represent predecessors to $CD16^{+}$ mature NK cells and can be seen both in the peripheral blood of pregnant women and enriched at the fetomaternal interface (Moffett-King 2002).

HLA-C is the only known polymorphic MHC or MHC-like molecule that is expressed by trophoblast cells and is the dominant ligand for the members of the KIR family of receptors that have two immunoglobulin-like domains (KIR2D). These might be activating (KIR2DS) or inhibitory (KIR2DL) receptors. KIR haplotypes comprise two groups, A and B. The main difference between them is that there are more activating receptors in the B haplotype. In any pregnancy, the maternal KIR genotype could be AA (no activating KIR) or AB/BB (presence of one to five activating KIRs). The HLA-C ligands for KIRs on trophoblast cells can belong to two groups, HLA-C1 and HLA-C2, which are defined by a dimorphism at position 80 of the 1st domain.

This maternal–fetal immunological interaction that occurs at the site of placentation, involves two polymorphic gene systems, maternal KIRs and fetal HLA-C molecules. NK-cell function is therefore likely to vary in each pregnancy. Some KIR/HLA-C combinations might be more favourable to trophoblast-cell invasion, resulting in a greater increase of the *in utero* placental blood flow than other combinations as a result of the overall signals that the NK cell receives (Moffet and Loke 2006).

A small proportion of decidual T cells also express the HLA-E specific CD94-NKG2A inhibitory and CD94-NKG2C activating receptors. Decidual KIR^{+} and $CD94\text{-}NKG2^{+}$ T cells mainly display a $CD3^{+}CD4^{-}CD8^{-}$ phenotype. However, decidual tissue also contains higher percentages of KIR and CD94-NKG2 expressing $CD4^{+}$ and $CD8^{+}$ T cells compared to peripheral blood. NK cell receptor expression on decidual T cells may provide an alternative means by which decidual T cells distinguish self (maternal) cells from allogeneic fetal cells, and act to modulate the decidual immune response (Tilburgs et al. 2009).

KIR-HLA-C genotype for NK cells may contribute to the immunological etiology of recurrent miscarriage (RM). In those species that have been studied in detail, such as humans and mice, there is no large influx of T or B cells to the implantation site in normal pregnancies. Any T cells present in failed pregnancies might be recruited following the demise of the fetus and the resulting inflammatory changes (Hong et al. 2008; Faridi and Agrawal 2011).

Decidual NK cells at the fetomaternal interface serve an immunoregulatory/angiogenic function to support placentation and are phenotypically identified by the expression of CD9, a tetraspanin involved in cell adhesion (Keskin et al. 2007).

Mature peripheral blood $CD16^+$ NK cells can be transformed into $CD16^-$ $CD9^+$ NK cells with a decidual phenotype after prolonged exposure to transforming growth factor-beta (TGF-β). Recently it has been discovered, that similar change of NK-cell population occurs, when the patients are suffering from metastatic melanoma (Holtan et al. 2011). A specific immune population namely **uterine natural killer (uNK) cells** has been shown to promote placentation and thus the establishment of a successful pregnancy through the production of cytokines, chemokines and angiogenic factors. The fetal portion of the placenta is comprised, in part, of trophoblast cells. In humans, fetal **extravillous trophoblast (EVT) cells** invade the uterus and the uterine spiral arteries and are thus in close proximity to maternal immune cells. EVT cells were shown to express class Ia HLA-C, too. Syncytiotrophoblast cells, which cover the chorionic villi have direct contact with maternal blood (Riley 2008; Riley and Yokoyama 2008). Trophoblasts are of fetal origin, i.e. semi-allogeneic because of the paternal genes and these have to escape the effects of the maternal immune system.

Natural killer (NK) cells represent the major lymphocyte population in the decidua basalis of the human uterus during healthy early pregnancy. The activity of **decidual NK (dNK) cells** and their activation status are different from those of **peripheral blood (PB)-NK cells**. Decidual NK cells have been defined as $CD56^{bright}$, $CD16^{neg}$, and more recently $CD160^{neg}$. They express a unique repertoire of NK cell receptors, identical among all donors tested. Decidual NK cells express in particular $NKp46^-$, $NKp30^-$ and $NKp44^-$activating receptors, contrasting with PB-NK cells which are devoid of NKp44-activating receptors. dNK cells cannot kill trophoblast cells during normal pregnancy because of the inhibitory potential of NKG2A. Whether such NKG2A-mediated inhibition is abolished during pregnancies complicated by pathologies including viral infection has not been revealed yet (El Costa et al. 2009).

Glycodelin A, secreted by the uterine mucosa and decidua is induced to high levels by progesterone between 12 and 16 weeks of pregnancy. The glycoprotein, an immunomodulator has been shown to be inhibitory to the survival and functions of almost all immune cells. The inhibition of cytotoxic T lymphocyte activity was brought about by the downregulation of transcription of the cytolytic effector molecules, granzyme B and perforin and the degranulation of cytolytic vesicles (SundarRaj et al. 2009; Soni and Karande 2010).

1.8 MHC-Class-II-Expressing Macrophages and Dendritic Cells (DCs)

These cells are also present in the placental bed and could present trophoblast-cell-derived antigens indirectly to the maternal immune system. These decidual antigen-presenting cells might be pivotal in the expansion of both $CD4^+CD25^+$ and $CD8^+$ regulatory T-cell populations that are present *in utero* during human

pregnancy. The $CD8^+$ regulatory T cells in the uterus are not MHC restricted but are specific for a member of the **carcinoembryonic antigen family**, an oncofetal trophoblast molecule, and selectively use the T-cell receptor V9. DC-10 represents a novel subset of tolerogenic DCs, which secrete high levels of IL-10, express ILT4 and HLA-G, and have the specific function to induce Tr1 cells (Gregori et al. 2010).

Monocytes and macrophages are most abundant maternal immune cells in the decidua basalis. They make up 20–30% of the decidual cells at the site of implantation which remains high throughout pregnancy. These cells regulate vascular grows, development of the placenta and are able to kill intracellular microbes, too. Monocyte/macrophages are activated by Th1 cytokines, such as IFN α and γ or bacterial lipopolysaccharides (LPS). In contrast to activation a "suppressive phenotype" which is induced by Th2 cytokines (IL4, IL10, IL13) and when they become linked with HLA-G molecules upon interaction with the trophoblast membranes at the maternal-fetal interface (Shakhawat et al. 2010).

1.9 Regulatory Immune Receptors of Trophoblast Cells

T cell activation requires engagement of the T cell receptors (TCR) with an antigenic peptide exposed by the major histocompatibility proteins. In addition to this TCR-generated signals, a costimulatory signal mediated through the interaction of members of the **B7 protein family** with the CD28 family of receptors is also required for naive T cell activation. The first members of this family identified were B7-1 (CD80) and B7-2 (CD86), which bind to both CD28 and/or CTLA-4. The binding of B7-1/B7-2 to CD28 generates a costimulatory signal, but the interaction with CTLA-4 leads to an inhibitory signal in activated T cells. B7-H1 is expressed in the human placenta throughout pregnancy and its expression increases as gestation progresses. B7-DC is consistently expressed on syncytiotrophoblast cells (Petroff et al. 2005).

The interaction between **inducible costimulator ICOS** and its ligand **ICOSL** is thought to regulate both Th1 and Th2 responses *in vivo*. CD28, a receptor for B7H1 and B7H2, is constitutively expressed on naive T cells, but ICOS is only up-regulated following T-cell receptor engagement and T-cell activation, and its expression in the peripheral blood is restricted to effector/memory T cells. *In vitro* stimulation by either ICOS or CD28 ligation promotes the production of interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) (Th1), interleukin (IL)-4, IL-13 (Th2) and IL-17 (Th17), but IL-2 release is only increased after CD28 ligation. On the other hand a critical role has been described for ICOS, but not for CD28 in IL-10 production, what is extremely important for the establishment of immunotolerance. Furthermore ICOS was consistently expressed at greater levels on the surface of $CD4^+$ and $CD8^+$ decidual T cells when compared with peripheral T cells. ICOS was found to be strongly expressed on decidual T_{REG} cells. T_{REG} cells

accumulate in the uterine decidua at a much higher density than that seen in the peripheral blood. The ICOS ligand, B7H2, was expressed on extra villous trophoblasts (EVTs) in the basal plate of term placentas. The ICOS-B7H2 pathway was suggested to play a role in antiviral defence. A subset of cytotoxic $CD8^+$ T cells can recognize peptides derived from pathogens, such as cytomegalovirus, that are bound to HLA-E molecules. The binding of B7H2 on EVTs to ICOS on decidual T cells may cooperate with antigen presentation by trophoblast-expressed HLA-E to promote Tcell activities that prevent uteroplacental infection (Nagamatsu et al. 2011).

Macrophages and T cells are inhibited through the interaction of **CD200 (OX2) and CD200R**. CD200 is expressed on endothelial cells, thymocytes, activated T cells, B cells, dendritic cells, osteoblasts, neurons and trophoblast cells. CD200R is expressed predominantly on myeloid cells but has also been detected on specific T cell populations, thus demonstrating a more restricted expression pattern than its ligand (Gorczynski et al. 2004; Wilczyński 2006).

Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) are highly glycosylated proteins that belong to the immunoglobulin superfamily of cell adhesion molecules (IgCAMs). CEACAM molecules help maintain tissue architecture and cell polarity. Secreted CEACAMs resembling immunomodulatory CEACAM1-related trophoblast-specific pregnancy-specific glycoproteins (PSGs) found in both humans and rodents evolved only in a limited set of mammals. The appearance of PSG-like genes correlates with invasive trophoblast growth in these species (Kammerer and Zimmermann 2010). At the early blastocyst stage of preimplantation development there are two cell lineages. The inner cell mass, which gives rise to the embryo while the trophectoderm cells develop into trophoblast cells and the fetal portion of the placenta. CEACAM1 was shown to be carried by extravillous trophoblast cells but not by villous cytotrophoblasts or syncytiotrophoblasts (Bamberger et al. 2000).

Proteomic analysis revealed high levels of soluble TNF receptor 1 in placenta, suggesting that blockade of the TNF-α pathway was a mechanism of disease suppression. Placenta contributed to the immune tolerance of pregnancy by locally inhibiting the TNF-α pathway (Landek-Salgado et al. 2011).

1.10 Maternal-Fetal Immunological Tolerance

Human $FoxP3^+CD4^+$ T cells can be separated into three functionally and phenotypically different subpopulations based on the expression of FoxP3, cell surface phenotype, the degree of DNA methylation of the FoxP3 gene, DNA microarray profile, proliferation status in the physiological state, cytokine secreting capacity, TCR repertoire, and in vitro suppressive activity. (1) $CD45RA^+FoxP3^{low}$ resting T_{REG} cells, (2) $CD45RA^-FoxP3^{high}$ activated T_{REG} cells, and (3) cytokine-secreting

$CD45RA^{-}FoxP3^{low}$ non-T_{REG} cells. With this dissection of $FoxP3^{+}$ T cells into subpopulations the dynamics of T_{REG} cell differentiation *in vitro, in vivo*, and *ex vivo* in normal and disease states may be understood. The results indicate that functional and numerical analysis of each $FoxP3^{+}$ subset is essential for assessing immunological states (Miyara et al. 2005, 2009). Naive T_{REG} cells were found to be resistant to CD95L induced apoptosis (Fritzsching et al. 2006).

Immune responses to infection are uniquely regulated during gestation to allow for antimicrobial defence and tissue repair, whilst preventing damage to developing fetal organs or the triggering of preterm labour. During fetal development, interleukin (IL)-23, IL-10 and IL-6, as well as T-helper-17 (Th17)-mediated immune responses, are upregulated, whereas tumour necrosis factor-α (TNF-α) and IL-1β- and Th1-mediated immune responses are downregulated in the intrauterine environment (both the fetal compartment and the amniotic compartment).

Infection-related immunity during gestation is preferentially directed towards combating extracellular microbial pathogens. Amniotic fluid and the neonatal circulation contain multiple components that improve the ability of the developing neonate to tolerate microbial-induced immune activation. The repertoire of immune mechanisms to control infection and inflammation differ between fetal and adult life. The dual mechanisms of resistance to infection and tolerance to infection-induced immune activation prevent damage to the developing fetus and the triggering of premature labour (Le Bouteiller et al. 2009; Witkin et al. 2011).

The embryo expresses paternal antigens foreign to the mother and therefore may be viewed as an allograft, yet in normal pregnancy the embryo does not undergo maternal immune rejection. A **Th1/Th2 ratio** increase has been linked to early pregnancy failure. Recently, $CD4^{+}CD25^{bright}Foxp3^{+}$ regulatory T_{REG} cells were recognized to play a crucial role in the maintenance of normal immune tolerance. These T_{REG} cells may also contribute to the maintenance of pregnancy. The emerging concept of the Th17/T_{REG} balance has challenged the conventional paradigm of Th1/Th2 hypothesis. $CD4^{+}$ interleukin (IL)-$17A^{+}$ T (Th17) cells and $CD4^{+}CD25^{bright}Foxp3^{+}$ regulatory T (T_{REG}) cells in peripheral blood were analyzed by flow cytometry; IL-17 concentrations in cell culture supernates were quantitatively determined by enzyme-linked immunosorbtion assay; and IL-17A positive cells in decidua tissues were measured by immunohistochemistry (Bettelli et al. 2006; Schumacher et al. 2007). Low serum interleukin 17 concentration was found to be associated with preterm birth (Hee et al. 2011). Human gammadelta T cells expressing the Vγ2Vδ2 T cell-receptors (TCR) play important roles in immune responses to microbial pathogens by monitoring prenyl pyrophosphate isoprenoid metabolites. Most adult Vγ2Vδ2 cells are memory cytotoxic cells that produce IFN-gamma. Recently, murine gammadelta T cells were found to be major sources of IL-17A in antimicrobial and autoimmune responses. IL-17A and IL-22 production by Vγ2Vδ2 cells were characterised, too. IL-17A-producing memory Vγ2Vδ2 cells exist at low but significant frequencies in adult humans (1:2762 T cells). Vγ2Vδ2 cells produce IL-22 (1:1864 T cells), although few

produce both IL-17A and IL-22. Many IL-17A + Vγ2Vδ2 cells of adult humans also produce IFN-gamma (Tgammadelta1/17). Human neonatal Vγ2Vδ2 cells stimulated with the bacterial Ag, (ε)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate, and various cytokines and mAbs in vitro resulted that IL-6, IL-1β, and TGF-β are required to generate Tgammadelta17 cells in neonates, whereas Tgammadelta1/17 cells additionally required IL-23. In adults, memory Tgammadelta1/17 and Tgammadelta17 cells required IL-23, IL-1β, and TGF-β, but not IL-6. IL-22-producing cells showed similar requirements. Both neonatal and adult IL-17A Vγ2Vδ2 cells expressed elevated levels of retinoid-related orphan receptor γ-T. These data suggested that, like Th17 alphabeta T cells, Vγ2Vδ2 T cells can be polarized into Tgammadelta17 and Tgammadelta1/17 populations with distinct cytokine requirements for their initial polarization and later maintenance (Ness-Schwickerath et al. 2010).

T_{REG} cells are defined as $CD4^+CD25^+Foxp3^+CD127^-$ lymphocytes. Among women who were not atopic, nulliparous women had lower percentages of T_{REG} cells over time compared with parous women. Atopic women with pets in the home during pregnancy had lower percentages of T_{REG} cells than atopic women who did not have pets. The trajectory was not affected by the other factors investigated. It was concluded by the authors that within women change in percentages of T_{REG} cells may vary by time in relation to delivery, as well as by maternal atopic status and exposure to pets and number of prior births. The data did not indicate an overall decline in T_{REG} cells in the postpartum period (Wegienka et al. 2011).

T_{REG} cells have demonstrated their ability to efficiently control autoimmune diseases. The number of T_{REG} cells decreases in several autoimmune diseases, and adoptive transfer of purified T_{REG} cells improves the autoimmune disorders (Crispin et al. 2003; Tang et al. 2004). Meanwhile, several studies have reported that T_{REG} frequencies in circulation increase during normal early pregnancy, peaking during the second trimester and then declining postpartum, and decrease in women with unexplained recurrent spontaneous abortion URSA (Yang et al. 2008a). It has been suggested that the enrichment of $CD4^+CD25^+T_{REG}$ in decidua may explain the local mechanisms of immunological tolerance and play a role in the maintenance of pregnancy. T_{REG} cells exert their function partly by secretion of anti-inflammatory cytokines IL-10 and TGF-β1 (Zheng et al. 2004; Awasthi et al. 2007). Additionally, TGF-β1 can promote Foxp3 expression by inducing T_{REG} differentiation from $CD4^+$ $CD25^-$ T cells.

Th17 cells expressing retinoic acid–related orphan receptor γ (ROR γ t) play critical roles in the development of autoimmunity and allergic reactions by producing IL-17. Th17 and T_{REG} cells have reciprocal developmental pathways and opposite effects, although T_{REG} cells can convert into Th17 cells in the inflammatory milieu *in vitro* and *in vivo* the requirement for the differentiation of naive CD4 T cells into effector T helper cells that produce IL-17 was the availability of costimulatory molecules CD28 and ICOS but was independent of the cytokines and transcription factors required for T helper type 1 or type 2 differentiation. IL-17 expression characterizes a unique T helper lineage that regulates tissue

inflammation (Park et al. 2005). Th17/T_{REG} subsets may therefore have evolved to induce or regulate tissue inflammation, analogous to the dichotomous Th1/Th2 T-cell subsets.

The proportions of Th17 cells and IL-17A concentration in peripheral blood in patients with URSA were significantly higher than those in non-pregnant women and normal pregnant women, providing evidence that Th17 cells may reverse the mechanisms mediating maternal immune tolerance of conceptus antigens and therefore may destroy the maintenance of pregnancy. IL-17F regulates pro-inflammatory gene expression *in vitro*, and this requires IL-17 receptor A, tumor necrosis factor receptor–associated factor 6, and Act1. *In vivo*, overexpression of IL-17F in lung epithelium led to infiltration of lymphocytes and macrophages and mucus hyperplasia in mice. IL-17F is an important regulator of inflammatory responses that seems to function differently than IL-17 in immune responses and diseases (Yang et al. 2008b).

The proportion of Th17 cells (see page 59) and IL-17A concentrations were both significantly higher in patients with unexplained recurrent spontaneous abortions (URSA) than in normal early pregnant (NEP) and non-pregnant (NP) persons. T_{REG} frequencies were significantly lower in patients with URSA than in NEP patients, and the ratio of Th17 to T_{REG} was significantly higher in the URSA group than in the other two. Additionally, the percentage of IL-17A cells in deciduas was significantly higher in patients with URSA than in NEP patients (Liu et al. 2010).

In decidua IL-17 was localized in both cytotrophoblast and syncytiotrophoblast cells of URSA and normal early pregnant patients. It is likely that Th17 cells also play a role in the local mechanisms of pregnancy. In addition, the decidua expressed more Th17 cells in patients with URSA than in normal early pregnant patients, further suggesting that Th17 cells destroy pregnancy. The vitamin A metabolites, including retinoic acid (RA), form ligands for retinoic acid-related nuclear receptors and together they play pleiotropic roles in various biological processes. RA also functions as a key modulator of transforming growth factor-beta (TGF-beta)-driven immune deviation, capable of suppressing the differentiation of interleukin-17 secreting T helper cells (TH17) and conversely promoting the generation of $Foxp3^+$ T regulatory (T_{REG}) cells. The role of RA in the reciprocal TGF-beta-driven differentiation of TH17 and T_{REG} is important also in the control a functional immune system, in particular at the mucosal interface of the intestine (Mucida et al. 2007, 2009).

It has been shown that IL-10 is not only required for the generation of virus-specific FoxP3 T cells but it also has a suppressive effect on the proliferation of virus-specific FoxP3CD8 T cells. These data are consistent with recent reports demonstrating in the lymphocytic choriomeningitis virus mouse model that IL-10 is a single key molecule that directly induces suppression of virus-specific CD8 T cells (Billerbeck et al. 2007).

The programmed death ligand 1 (PDL-1) and the PD-1-PDL-1 axis is thought to maintain peripheral tolerance at the fetomaternal interface together with the T_{REG} cells (Guleria et al. 2005; Habicht et al. 2007). The expression of PDL-1 in human placenta by villous syncytiotrophoblasts and cytotrophoblast, the fetal cells that lie

in close contact with maternal blood and tissue makes it possible for this pathway to be critical in local immune response in vivo during pregnancy (Okazaki and Honjo 2006; Petroff et al. 2003, 2005). PD-1 but not CTLA-4 was found to abrogate the effect of TREG cells in mice (Wafula et al. 2009). PD-1-PCD-1 regulate accumulation of human fetal antigen-specific $CD8^+$ T cells, too (Taglauer et al. 2008, 2009).

1.11 Toll-Like Receptors at the Maternal-Fetal Interface

A family of **pattern recognition receptors (PRR)** is representing the innate immunity and are called **toll-like receptors (TLRs)**. These are expressed not only in the immune cells but also in non-immune cells such as trophoblasts and decidual cells; moreover, their expression patterns vary according to the stage of pregnancy. PRR and TLRs were shown to be activated as a network of different consequences i.e. inflammation, stimulation or immunemodulation (Heil et al. 2004; Kumazaki et al. 2004; Trinchieri and Sher 2007).

Immature NK cells were detected at the fetomaternal interface in NOD/SCID mice. These cells were hyposensitive to the stimulation of selected TLR agonists. Such a status seemed to be beneficial for the maintenance of pregnancy (Lin et al. 2009).

In the human placenta, however, TLR ligand-exposed trophoblasts, compared to controls, secrete more proinflammatory cytokines and chemokines to enhance immune cell migration (Koga et al. 2009).

At term, TLR activation by a yet unknown ligand may lead to the production of proinflammatory cytokines (IL-1, 6 and 8) and prostaglandin synthesis resulting in cervical ripening, membrane rupture, and uterine contractions resulting in the induction of labor. Prior to term, bacterial products such as LPS may induce the same cascade of events by activating TLRs leading to preterm labor (Riley and Nelson 2010).

Table 1.3 Specificity and localisation of Toll-like receptors (Koga and Mor 2008; Riley and Nelson 2010)

Cytoplasmic membrane	Endoplasmic reticulum membrane	Ligands	References
TLR-1/2		Triacyl lipopeptides, glycolipids	Triantafilou et al. (2006)
TLR-2/6		Diacyl lipopeptides, lipotechoic acid, zymozan	Aliprantis et al. (1999, 2000)
	TLR-3/TRIF-IRF3	Double stranded RNA	Alexopoulou et al. (2001)
TLR-4		LPS, envelop proteins, glycoinositol phospholipids, mannan	Beijar et al. (2006) and Kumazaki et al. (2004)
TLR-5		Flagellins	Patni et al. (2009)
	TLR-7	Single stranded RNA	Diebold et al. (2004)
	TLR-8	Single stranded RNA	Heil et al. (2004)
	TLR-9	Unmethylated CpG DNA	Lund et al. (2003), HSV
TLR-11		Profilin of protozoa	Yarovinsky et al. (2005)

Intracellular inducer (poly I:C for TLR 3) is only able to induce the production of RANTES and NF-κB if it is packed into liposomes in order to rich the endosomal receptor. This RANTES production was abolished by siRNA for TLR3 indicating the specificity of the induction (Nakada et al. 2009, 2011, Gonzalez et al. 2007). The Toll-like receptors, their location of their expression and the main inducers are summarised in Table 1.3.

1.12 Complement Activation and Pregnancy

Activation of the classical or lectin pathway (C4d) of complement activation showed significant positive correlation to C3 activation (C3a) both in healthy pregnant women and preeclamptic patients. However, the correlation between C3 and the terminal pathway activation was dominating only in patients with preeclampsia, but not in healthy pregnant women. During pregnancy the complement system is activated through the classical pathway and/or lectin pathway with increased terminal complex formation both in the third trimester of normal pregnancy, and to a further extent in preeclampsia, as indicated by the elevated concentrations of activation markers in the systemic circulation. Excessive activation of the terminal pathway is associated with fetal growth restriction in preeclamptic women (Derzsy et al. 2010; Csuka et al. 2010).

Freshly isolated human first trimester trophoblast cells (CTBs) synthesize complement molecules C4, C3 and the late complement components and HTR8/SVneo trophoblast cells secrete C6 in a measurable amount. HTR8/SVneo trophoblast cells secrete C6 in a measurable amount. The production of complement components was up-regulated by IFNgamma, while IL-1alpha and TNFalpha had no effect on their expression. Complement synthesis by trophoblast cells potentially contributes to placental immune defence from pathogen infection (Bulla et al. 2009).

Uncontrolled complement activation puts at risk the survival of the fetus detected in mouse models of recurrent miscarriages and preeclampsia. Increased circulating levels of complement proteins, and their activation fragments were found in patients with preeclampsia, recurrent miscarriages and intrauterine growth restriction. C1q deserves special consideration for its role in promoting trophoblast invasion of deciduas, a crucial step in normal placental development (Girardi et al. 2011). Autoantibodies to C1q were reacted in both healthy and diseased people with the globular part of C1q indicating that the onset of IgG mediated autoimmune response might occur when the molecule has interacted with its ligands via the globular-subunit-B as part of gC1q (Stoyanova et al. 2011).

Eculizumab a humanised monoclonal antibody which prevents the hydrolysis of C5 was found to prevent maternal hemolytic illnesses, without impairment of the development of the fetus (Kelly et al. 2010).

1.13 The Prevention of Fetal Damage by Inhibitory Asymmetric Maternal Antibodies

Specific antibodies, unable to precipitate soluble antigens have been observed many years ago (Heidelberger and Kendall 1935). Asymmetric IgG was shown to be the consequence of assymmetric presence of a carbohydrate moiety on one of the Fab fragments. This modification prevents the activation of complement, cytotoxic activity, opsonising ability, antigen clearance and precipitating activity of the molecules. The proportion of asymmetric IgG was much higher, averaging 44.4% in the case of antibodies extracted from the human placenta.

Antipaternal antibodies were detected in the sera of seven of ten pregnant women. The concentration of antipaternal antibodies was about three times higher in the asymmetric IgG fraction than in the symmetric one. It has been suggested, that asymmetric IgG molecules with antipaternal antigen specificity might function as blocking antibodies in order to prevent possible impairment of the fetus (Malan Borel et al. 1991). Hybridoma cell lines OKT8 (anti-CD8) and 112B4 (anti-DNP) are synthesising both symmetric and asymmetric molecules of the IgG2a and IgG1 subclasses in which anti-paternal antibodies have been detected. In the presence of 5–10% placental supernatant in the culture medium the proportion of asymmetric antibodies increased from 15–17% to 27–28% indicating its possible stimulatory effect to the cell lines (Margni et al. 1992; Margni and Malan Borel 1998).

Progesteron induced blocking factor (PIBF) was shown to enhance production of Th2-type cytokines; thus, it might stimulate also antibody production of B-cells. The ratio of asymmetric IgG was significantly higher in the supernates of hybridoma cells in the presence of PIBF in comparison to cells without PIBF in the medium. Blocking of PIBF receptors by inhibitors or treatment of the cells with PIBF receptor-specific antibodies prevented the excess production of asymmetric antibodies (Kelemen et al. 1996).

The proportion of asymmetric tetanus and diphteria antitoxins were 3–5 times higher in pregnants, than in nonpregnant women. The difference disappeared about 1 month after delivery. The concentration of asymmetric cord blood antibodies was found to be also 4–5 times elevated, indicating that the transplacental transfer had not been influenced by the asymmetric nature of IgG (Pasetti et al. 1997). The cytokine combination IL-4 + IL-10 + IL-6 stimulated the asymmetric IgG production to the highest degree. The authors observed, that the maternal lymphocytes could be better stimulated than the lymphocytes of the cord blood (Canellada et al. 2002). IL-6 was found to regulate directly the synthesis of asymmetric IgG populations in the B-cells during pregnancy (Gutiérrez et al. 2001).

Good correlation was observed in women with recurrent early abortions of unknown etiology, between the production of **anti-husband lymphocytes** and the success of a subsequent pregnancy. Women who suffered from recurrent spontaneous abortions of unknown etiology, without autoimmune abnormalities and without antipaternal antibodies, was found to profit from a therapy using the husband's leucocyte infusions, which allowed them to give birth to a normal child in 85% of the cases, whereas without treatment the success rate was only 37% of the pregnancies

(Reznikoff-Etievant 1988). Increased production of placental isoferritin seemed to be the explanation of the increased immunosuppression (Moroz et al. 1993).

Regulatory T cells act in an antigen-specific manner during pregnancy and mouse experiments strongly suggest that IL-10 is involved in regulatory T cell-mediated protection of the fetus. These data contribute to the knowledge of the basic mechanisms regulating immune tolerance during pregnancy, a major biologic question with important medical implications. Japanese physicians have observed, that the incidence of abortions of the same women is 20% higher in the case of pregnancies from a second husband than from the first one.

1.14 Virus Infections of Trophoblasts, Placenta and Fetus

Herpes simplex type 2 (HSV-2) and echovirus-19 replicated in placental macrophages in vitro (Oliveira et al. 1993). SV-40 polyomavirus was seen to replicate in extravillous trophoblasts and the inhibition of metalloproteinase expression impaired invasive potential of the cells (Logan et al. 1996). BK polyomavirus can infect several fetal organs, but was not found to be responsible for abortions (Boldorini et al. 2010). It has been revealed, that the herpes simplex type 1 and HCMV infection influence the expression of HLA-A and B antigens, but the expression of HLA-C and -G in the infected trophoblast cells decreases (Schust et al. 1999). Exacerbation of herpes simplex virus infection during pregnancy is associated with damage to syncytiotrophoblast inflicted by herpesvirus either directly or via TNF-α (due to contact of NK lymphocytes with villus surface). A sharp decrease in the content of heat shock protein with a molecular weight of 70 kDa and activation of caspase-3 were noted in placenta homogenates. This may lead to disturbances in syncytiotrophoblast cytosol structure and increase the relative content of apoptotic nuclei (Lutsenko et al. 2010). Human cytomegalovirus HCMV can infect villus trophoblasts in vitro and cause the decrease of early pregnancy villous EVT's invasive function (Tao et al. 2011). Indoleamine 2,3-dioxygenase (IDO) is highly expressed in the placenta and is known to prevent maternal immune rejection. HCMV infection inhibited IDO activity in the early placenta. IFN-γ-induced IDO activity was suppressed by HCMV in both early and term placenta. Early placental dysfunction through the inhibition of IDO activity may reveal a possible mechanism for miscarriages (Lopez et al. 2011). Epstei-Barr virus (EBV) can replicate ex vivo in syncytiotrophoblast cells (Tóth et al. 1997). HCMV, HHSV, HHV-6, and-7 and B-19 parvovirus were found in samples taken from abortions or unexplained fetal death in utero (Al-Buhtori et al. 2011). Hepattis B virus (HBV) can replicate in trophoblast cells ex vivo (Zhang et al. 2011). The presence of adeno-associated Dependovirus (AAV) in decidual or trophoblastic cells in cases of abortion implies that the virus could have causal association and abortion. The occurrence of AAV was found to be much higher the case of abortions than in the saples taken from intentional abortions (Pereira et al. 2010). Human bocavirus (HBoV) seropositivity was found to be very frequent in pregnants, but this virus was not shown to harm the offspring (Enders

et al. 2009). The globosid receptor for human parvovirus B-19 was found to be expressed in syncytiotrophoblast cells (Wegner and Jordan 2004). B-19 parvovirus was also found in samples taken from abortions or unexplained fetal death in utero (Al-Buhtori et al. 2011). Human endogenous retrovirus W (HERV-W) was expressed in syncytiotrophoblast cells, and the envelope proteins (syncytin 1 and 2) induce the fusion of cytotrophoblast cells (Malden et al. 2000; Mi et al. 2000; Blaise et al. 2005; Noorali et al. 2009; Vargas et al. 2009). *Ex vivo*, **human herpesvirus 8 (HHV-8)** DNA and a latent viral antigen were detected in placental samples from HHV-8-seropositive women. These findings demonstrate that HHV-8, like other human herpesviruses, may infect placental cells *in vitro* and *in vivo* (Di Stefano et al. 2008). Vertical transmission may occur through $CD4^+$ endothelial tissues or $CD4^+$ fetal Hofbauer cells. Trophoblasts and floating villi have CD4-receptors, which make them potential candidates for **human immunodeficiency virus (HIV)** infection. Placental cytokines and chemokines influence **HIV** replication in trophoblasts. Genetic analysis of HIV-1 sequences verify the interaction of HIV-1 and placental tissue. The vertical transmission of HIV-1 characterized by selection of genotype variant that escape the mother's immune system (Vidricaire and Tremblay 2007; Al-Husaini 2009). Interleukin 6 and tumor necrosis factor α were shown to potentiate HIV-1 replication in explants of syncytiotrophoblasts (Bácsi et al. 2001). **HIV-infected women** display different immunologic profiles from HIV-negative women, which may have importance for the induction of fetal-maternal tolerance and in part explain the increased risk of abortion in HIV-infected women (Kolte et al. 2011). The presence of **papillomaviruses** in the cord blood shows, that these are also able to pass the maternal-fetal barrier (Hermonat et al. 1998; Younes et al. 2007, 2009; You et al. 2008; Sarkola et al. 2008). The Hungarian Case-control Surveillance of Congenital Abnormalities dataset (1980–1996) comprises records of 22,843 neonates with different specified congenital abnormalities, and 38,151 matched controls without defects. A total of 17 (0.07%) mothers of neonates with abnormalities and 25 (0.07%) mothers of neonates without defects were affected by genital warts during the study pregnancy indicating that papillomaviruses do not play a role in the development of fetal abnormalities (Bánhidy et al. 2010). **West Nile** virus was also able to multiply in trophoblast cells (Julander et al. 2006). Human T-cell leukemiavirus (**HTLV-1 and HHV-6**) and human herpesvirus 6 (Csoma et al. 2002). **Coxsackieviruses** can replicate in trophoblast cells, too (Euscher et al. 2001). **Measles virus** was shown to replicate in the placenta in twins of unvaccinated mothers (Ohyama et al. 2001). The different subgenera of **rubellavirus** were suggested to affect the fetuses i.e. the most isolates in France belonged to subgenus "E" (Vauloup-Fellous et al. 2010). Death of the mother and fetus, abortion, premature delivery, or death of a live-born baby soon after birth are common complications of **Hepatitis E virus (HEV)** infection during pregnancy (Smith 2001). **Rift valley fever virus (RVFV)** is causing frequently abortions (Ikegami and Makino 2011).

Some viral infections during pregnancy may be asymptomatic, about one-half of all preterm deliveries were associated with histological evidence of inflammation of the placenta, i.e. acute or chronic chorioamnionitis. **Even in the absence of fetal**

viral infection, the inflammatory response originating in the placenta and decidua induced an inflammatory process with potential damage in fetal organs (Cardenas et al. 2010). One factor of the impairment of fetal development and of the formation of multiple congenital abnormality syndrome is the high fever of the women during pregnancy (Czeizel et al. 2008). Pelvic inflammatory diseases during pregnancy were shown to induce fetal malformations detected on the basis of a population-based case-control study (Ács et al. 2008).

In contrast to the numerous preventive functions of the maternal-fetal barriers, about 5% of the pregnancies suffer irreversible impairments. These are summarised in Table 1.2. based on the excellent review of Pandey et al. (2005).

References

Ács N, Bánhidy F, Puhó EH, Czeizel AE (2008) Possible association between acute pelvic inflammatory disease in pregnant women and congenital abnormalities in their offspring: a population-based case-control study. Birth Defects Res A Clin Mol Teratol 82:563–570

Adachi H, Takakuwa K, Mitsui T, Ishii K, Tamura M, Tanaka K (2003) Results of immunotherapy for patients with unexplained secondary abortions. Clin Immunol 106:175–180. doi:10.1016/S1521-6616(02)00044-X

Al-Buhtori M, Moore L, Benbow EW, Cooper RJ (2011) Viral detection in hydrops fetalis, spontaneous abortion, and unexplained fetal death in utero. J Med Virol 83:679–684. doi:10.1002/jmv.22007

Aldrich CL, Stephenson MD, Karrison T, Odem RR, Branch DW, Scott JR, Schreiber JR, Ober C (2001) HLA-G genotypes and pregnancy outcome in couples with unexplained recurrent miscarriage. Mol Hum Reprod 7:1167–1172. doi:10.1093/molehr/7.12.1167

Alexopoulou L, Holt AC, Medzhitov R, Flavell RA (2001) Recognition of double-stranded RNA and activation of NF-kappaB by toll-like receptor 3. Nature 413:732–738. doi:10.1038/35099560

Al-Husaini AM (2009) Role of placenta in the vertical transmission of human immunodeficiency virus. J Perinatol 29:331–336, Review

Ali RS, Falconer A, Ikram M, Bissett CE, Cerio R, Quinn AG (2001) Expression of the peptide antibiotics human beta defensin-1 and human beta defensin-2 in normal human skin. J Invest Dermatol 117:106–111. doi:10.1046/j.0022-202x.2001.01401.x

Aliprantis AO, Yang R-B, Mark MR, Suggett S, Devaux B, Radolf JD, Klimpel GR, Godowski P, Zychlinsky A (1999) Cell activation and apoptosis by bacterial lipoproteins through toll-like receptor-2. Science 285:736–739. doi:10.1126/science.285.5428.736

Aliprantis AO, Yang RB, Weiss DS, Godowski P, Zychlinsky A (2000) The apoptotic signaling pathway activated by toll-like receptor-2. EMBO J 19:3325–3336. doi:10.1093/emboj/19.13.3325

Apps R, Gardner L, Sharkey AM, Holmes N, Moffett A (2007) A homodimeric complex of HLA G on normal trophoblast modulates antigen presenting cells via LILRB1. Eur J Immunol 37:1924–1937. doi:10.1002/eji.200737089

Armah HB, Wang G, Omalu BI, Tesh RB, Gyure KA, Chute DJ, Smith RD, Dulai P, Vinters HV, Kleinschmidt-DeMasters BK, Wiley CA (2007) Systemic distribution of West Nile virus infection: postmortem immunohistochemical study of six cases. Brain Pathol 17:354–362. doi:10.1111/j.1750-3639.2007.00080.x

Arthos J, Cicala C, Martinelli E, Macleod K, Van Ryk D, Wei D, Xiao Z, Veenstra TD, Conrad TP, Lempicki RA, McLaughlin S, Pascuccio M, Gopaul R, McNally J, Cruz CC, Censoplano N, Chung E, Reitano KN, Kottilil S, Goode DJ, Fauci AS (2008) HIV-1 envelope protein binds to

and signals through integrin alpha(4)beta(7), the gut mucosal homing receptor for peripheral T cells. Nat Immunol 9:301–309. doi:10.1038/ni1566

Awasthi A, Carrier Y, Peron JP, Bettelli E, Kamanaka M, Flavell RA, Kuchroo VK, Oukka M, Weiner HL (2007) A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells. Nat Immunol 8:1380–1389. doi:10.1038/ni1541

Bácsi A, Csoma E, Beck Z, Andirkó I, Kónya J, Gergely L, Tóth FD (2001) Induction of HIV-1 replication in latently infected syncytiotrophoblast cells by contact with placental macrophages: role of interleukin-6 and tumor necrosis factor-alpha. J Interferon Cytokine Res 21:1079–1088. doi:10.1089/107999001317205213

Bainbridge DR, Ellis SA, Sargent IL (2000a) HLA-G suppresses proliferation of CD4(+) T-lymphocytes. J Reprod Immunol 48:17–26. doi:10.1016/S0165-0378(00)00070-X

Bainbridge DR, Ellis SA, Sargent IL (2000b) The short forms of HLA-G are unlikely to play a role in pregnancy because they are not expressed at the cell surface. J Reprod Immunol 47:1–16. doi:10.1016/S0165-0378(00)00056-5

Baldassarre M, Fanelli M, Corvaglia L, Laforgia N (2011) Longitudinally evaluation of human-beta defensins and Tumor necrosis factor- alfa in stools of preterm and term newborns. J Pediatr Gastroenterol Nutr 53(5):582. doi:10.1097/MPG.0b013e31822c92f0

Bamberger AM, Sudahl S, Loning T, Wagener C, Bamberger CM, Drakakis P, Coutifaris C, Makrigiannakis A (2000) The adhesion molecule CEACAM1 (CD66a, C-CAM, BGP) is specifically expressed by the extravillous intermediate trophoblast. Am J Pathol 156:1165–1170. doi:10.1016/S0002-9440(10)64985-1

Bánhidy F, Acs N, Puhó EH, Czeizel AE (2010) Birth outcomes among pregnant women with genital warts. Int J Gynaecol Obstet 108:153–154. doi:10.1016/j.ijgo.2009.09.010

Bargatze RF, Jutila MA, Butcher EC (1995) Distinct roles of L-selectin and integrins alpha 4 beta 7 and LFA-1 in lymphocyte homing to Peyer's patch-HEV in situ: the multistep model confirmed and refined. Immunity 3:99–108

Beijar EC, Mallard C, Powell TL (2006) Expression and subcellular localization of TLR-4 in term and first trimester human placenta. Placenta 27:322–326. doi:10.1016/j.placenta.2004.12.012

Berencsi G, Kereszti Z (1976) Effect of chemicals on rabbits when injected into the testicles. Differences in effects depending on mode of application (author's transl) [German]. Arzneimittelforschung 26:2048–2050

Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK (2006) Reciprocal developmental pathways for the generation of pathogenic effector or TH17 and regulatory T cells. Nature 441:235–238

Beyer U, Moll-Rocek J, Moll UM, Dobbelstein M (2011) Endogenous retrovirus drives hitherto unknown proapoptotic p63 isoforms in the male germ line of humans and great apes. Proc Natl Acad Sci U S A 108:3624–3629. doi:10.1073/pnas.1016201108

Biagioli MC, Kaul P, Singh I, Turner RB (1999) The role of oxidative stress in rhinovirus induced elaboration of IL-8 by respiratory epithelial cells. Free Radic Biol Med. 26(3–4):454–462

Billerbeck E, Blum HE, Thimme R (2007) Parallel expansion of human virus-specific FoxP3-effector memory and de novo-generated FoxP3+ regulatory CD8+ T cells upon antigen recognition in vitro. J Immunol 179:1039–1048

Blaise S, de Parseval N, Heidmann T (2005) Functional characterization of two newly identified Human Endogenous Retrovirus coding envelope genes. Retrovirology 2:19. doi:10.1186/1742-4690-2-19

Boldorini R, Allegrini S, Miglio U, Nestasio I, Paganotti A, Veggiani C, Monga G, Pietropaolo V (2010) BK virus sequences in specimens from aborted fetuses. J Med Virol 82:2127–2132. doi:10.1002/jmv.21923

Bozym RA, Morosky SA, Kim KS, Cherry S, Coyne CB (2010) Release of intracellular calcium stores facilitates coxsackievirus entry into polarized endothelial cells. PLoS Pathog 6 pii: e1001135. doi:10.1371/journal.ppat.1001135

Brandtzaeg P (2010) Homeostatic impact of indigenous microbiota and secretory immunity. Benef Microbes 1:211–227. doi:10.3920/BM2010.0009

Bulla R, Bossi F, Agostinis C, Radillo O, Colombo F, De Seta F, Tedesco F (2009) Complement production by trophoblast cells at the feto-maternal interface. J Reprod Immunol 82:119–125. doi:10.1016/j.jri.2009.06.124

Camacho EM, Farragher TM, Lunt M, Verstappen SM, Bunn D, Symmons DP (2010) The relationship between post-onset pregnancy and functional outcome in women with recent onset inflammatory polyarthritis: results from the Norfolk Arthritis Register. Ann Rheum Dis 69:1834–1837. doi:10.1136/ard.2010.128769

Canellada A, Färber A, Zenclussen AC, Gentile T, Dokmetjian J, Keil A, Blois S, Miranda S, Berod L, Gutiérrez G, Markert UR, Margni RA (2002) Interleukin regulation of asymmetric antibody synthesized by isolated placental B cells. Am J Reprod Immunol 48:275–282. doi:10.1034/j.1600-0897.2002.01125.x

Cardenas I, Means RE, Aldo P, Koga K, Lang SM, Booth C, Manzur A, Oyarzun E, Romero R, Mor G (2010) Viral infection of the placenta leads to fetal inflammation and sensitization to bacterial products predisposing to preterm labor. J Immunol 185:1248–1257. doi:10.4049/jimmunol.1000289

Carosella ED, Moreau P, Le Maoult J, Le Discorde M, Dausset J, Rouas-Freiss N (2003) HLA-G molecules: from maternal-fetal tolerance to tissue acceptance. Adv Immunol 81:199. doi:10.1016/S0065-2776(03)81006-4

Castelli EC, Moreau P, Oya e Chiromatzo A, Mendes-Junior CT, Veiga-Castelli LC, Yaghi L, Giuliatti S, Carosella ED, Donadi EA (2009) In silico analysis of microRNAS targeting the HLA-G 3′ untranslated region alleles and haplotypes. Hum Immunol 70:1020–1025. doi:10.1016/j.humimm.2009.07.028

Castelli EC, Mendes-Junior CT, Deghaide NH, de Albuquerque RS, Muniz YC, Simões RT, Carosella ED, Moreau P, Donadi EA (2010) The genetic structure of 3′untranslated region of the HLA-G gene: polymorphisms and haplotypes. Genes Immun 11:134–141

Castelli EC, Mendes-Junior CT, Veiga-Castelli LC, Roger M, Moreau P, Donadi EA (2011) A comprehensive study of polymorphic sites along the HLA-G gene: implication for gene regulation and evolution. Mol Biol Evol. 28(11):3069–3086.

Cervera I, Herraiz MA, Peñaloza J, Barbolla ML, Jurado ML, Macedo J, Vidart J, Martinez-Laso J (2010) Human leukocyte antigen-G allele polymorphisms have evolved following three different evolutionary lineages based on intron sequences. Hum Immunol 71(11):1109–1115. doi:10.1016/j.humimm.2010.07.003

Cervera I, Herraiz MA, Penaloza J, Vidart J, Martinez-Laso J (2011) The novel HLA-G*01:03:01:02 allele differs from G*01:03:01:01 by a possible inversion event in intron 3. Tissue Antigens 78:159–160. doi:10.1111/j.1399-0039.2011.01678.x

Chaithanyaa N, Devireddy SK, Kishore Kumar RV, Gali RS, Aneja V (2011) Sympathetic ophthalmia: a review of literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod Apr 14. doi:10.1016/j.tripleo.2011.01.036

Chan CK, Limstrom SA, Tarasewicz DG, Lin SG (2006) Ocular features of west nile virus infection in North America: a study of 14 eyes. Ophthalmology 113:1539–1546. doi:10.1016/j.ophtha.2006.04.021

Chen HX, Chen BG, Shi WW, Zhen R, Xu DP, Lin A, Yan WH (2011) Induction of cell surface human leukocyte antigen-G expression in pandemic H1N1 2009 and seasonal H1N1 influenza virus-infected patients. Hum Immunol 72:159–165. doi:10.1016/j.humimm.2010.11.009

Clark RA, Chong BF, Mirchandani N, Yamanaka KI, Murphy GF, Dowgiert RK, Kupper TS (2006a) A novel method for the isolation of skin resident T cells from normal and diseased human skin. J Invest Dermatol 126:1059–1070. doi:10.1038/sj.jid.5700199

Clark RA, Chong B, Mirchandani N, Brinster NK, Yamanaka KI, Dowgiert RK, Kupper TS (2006b) The vast majority of CLA + T cells are resident in normal skin. J Immunol 176:4431–4439

Clifford K, Rai R, Watson H, Regan L (1994) An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. Hum Reprod 9:1328–1332

Cohen-Solal J, Diamond B (2011) Lessons from an anti-DNA autoantibody. Mol Immunol 48:1328–1331. doi:10.1016/j.molimm.2010.12.003

Comstock AT, Ganesan S, Chattoraj A, Faris AN, Margolis BL, Hershenson MB, Sajjan US (2011) Rhinovirus-induced barrier dysfunction in polarized airway epithelial cells is mediated by NADPH oxidase 1. J Virol 85:6795–6808. doi:10.1128/JVI.02074-10

Corthésy B (2007) Roundtrip ticket for secretory IgA: role in mucosal homeostasis? J Immunol 178:27–32

Coyne CB, Bergelson JM (2006) Virus-induced Abl and Fyn kinase signals permit coxsackievirus entry through epithelial tight junctions. Cell 124:119–131. doi:10.1016/j.cell.2005.10.035

Crispin JC, Martinez A, Alcocer-Varela J (2003) Quantification of regulatory T cells in patients with systemic lupus erythematosus. J Autoimmun 21:273–276. doi:10.1016/S0896-8411(03)00121-5

Csoma E, Bácsi A, Liu X, Szabó J, Ebbesen P, Beck Z, Kónya J, Andirkó I, Nagy E (2002) Tóth FD Human herpesvirus 6 variant a infects human term syncytiotrophoblasts in vitro and induces replication of human immunodeficiency virus type 1 in dually infected cells. J Med Virol 67:67–87. doi:10.1002/jmv.2194

Csomor E, Bajtay Z, Sandor N, Kristof K, Arlaud GJ, Thiel S, Erdei A (2007) Complement protein C1q induces maturation of human dendritic cells. Mol Immunol 44:3389–3397. doi:10.1016/j.molimm.2007.02.014

Csuka D, Molvarec A, Derzsy Z, Varga L, Füst G, Rigó J Jr, Prohászka Z (2010) Functional analysis of the mannose-binding lectin complement pathway in normal pregnancy and pre-eclampsia. J Reprod Immunol 87:90–96. doi:10.1016/j.jri.2010.07.004

Czeizel AE, Puhó EH, Acs N, Bánhidy F (2008) Delineation of a multiple congenital abnormality syndrome in the offspring of pregnant women affected with high fever-related disorders: a population-based study. Congenit Anom (Kyoto) 48:158–166. doi:10.1111/j.1741-4520.2008.00202.x

Dawe GS, Tan XW, Xiao ZC (2007) Cell migration from baby to mother. Cell Adh Migr 1:19–27, Review

de Jong MA, Geijtenbeek TB (2010) Langerhans cells in innate defense against pathogens. Trends Immunol 31:452–459. doi:10.1016/j.it.2010.08.002

de Witte L, Nabatov A, Pion M, Fluitsma D, de Jong MA, de Gruijl T, Piguet V, van Kooyk Y, Geijtenbeek TB (2007) Langerin is a natural barrier to HIV-1 transmission by Langerhans cells. Nat Med 13:367–371. doi:10.1038/nm1541

de Witte L, Nabatov A, Geijtenbeek TB (2008) Distinct roles for DC-SIGN + -dendritic cells and Langerhans cells in HIV-1 transmission. Trends Mol Med 14:12–19. doi:10.1016/j.molmed.2007.11.001, Review

Derzsy Z, Prohászka Z, Rigó J Jr, Füst G, Molvarec A (2010) Activation of the complement system in normal pregnancy and preeclampsia. Mol Immunol 47:1500–1506. doi:10.1016/j.molimm.2010.01.021

Di Stefano M, Calabrò ML, Di Gangi IM, Cantatore S, Barbierato M, Bergamo E, Kfutwah AJ, Neri M, Chieco-Bianchi L, Greco P, Gesualdo L, Ayouba A, Menu E, Fiore JR (2008) In vitro and in vivo human herpesvirus 8 infection of placenta. PLoS One 3:e4073. doi:10.1371/journal.pone.0004073

Diebold SS, Kaisho T, Hemmi H, Akira S, Reis e Sousa C (2004) Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. Science 303:1529–1531. doi:10.1126/science.1093616

Diepstra A, Poppema S, Boot M, Visser L, Nolte IM, Niens M, Te Meerman GJ, van den Berg A (2008) HLA-G protein expression as a potential immune escape mechanism in classical Hodgkin's lymphoma. Tissue Antigens 71:219–226. doi:10.1111/j.1399-0039.2008.01005.x

Donadi EA, Castelli EC, Arnaiz-Villena A, Roger M, Rey D, Moreau P (2011) Implications of the polymorphism of HLA-G on its function, regulation, evolution and disease association. Cell Mol Life Sci 68:369–395, Review

Dulin JN, Moore ML, Gates KW, Queen JH, Grill RJ (2011) Spinal cord injury causes sustained disruption of the blood-testis barrier in the rat. PLoS One 6:e16456. doi:10.1371/journal.pone.0016456

Eberwein P, Hansen LL, Agostini HT (2005) Genotypes of JC virus, DNA of cytomegalovirus, and proviral DNA of human immunodeficiency virus in eyes of acquired immunodeficiency syndrome patients. J Neurovirol 11:58–65. doi:10.1080/13550280590900391

Ebihara N, Chen L, Tokura T, Ushio H, Iwatsu M, Murakami A (2007) Distinct functions between toll-like receptors 3 and 9 in retinal pigment epithelial cells. Ophthalmic Res 39:155–163. doi:10.1159/000103235

Eblen AC, Gercel-Taylor C, Shields LB, Sanfilippo JS, Nakajima ST, Taylor DD (2000) Alterations in humoral immune responses associated with recurrent pregnancy loss. Fertil Steril 73:305–313. doi:10.1016/S0015-0282(99)00505-1

El Costa H, Tabiasco J, Berrebi A, Parant O, Aguerre-Girr M, Piccinni M-P, Le Bouteilleremail P (2009) Effector functions of human decidual NK cells in healthy early pregnancy are dependent on the specific engagement of natural cytotoxicity receptors. J Reprod Immunol 82:142–147. doi:10.1016/j.jri.2009.06.123

Enders M, Lindner J, Wenzel JJ, Baisch C, Schalasta G, Enders G, Modrow S (2009) No detection of human bocavirus in amniotic fluid samples from fetuses with hydrops or isolated effusions. J Clin Virol 45:300–303. doi:10.1016/j.jcv.2009.04.005

Engelter ST, Provenzale JM, Petrella JR (2000) Assessment of vasogenic edema in eclampsia using diffusion imaging. Neuroradiology 42:818–820. doi:10.1007/s002340000439

Euscher E, Davis J, Holzman I, Nuovo GJ (2001) Coxsackie virus infection of the placenta associated with neurodevelopmental delays in the newborn. Obstet Gynecol 98:1019–1026. doi:10.1016/S0029-7844(01)01625-8

Faridi RM, Agrawal S (2011) Killer immunoglobulin-like receptors (KIRs) and HLA-C allorecognition patterns implicative of dominant activation of natural killer cells contribute to recurrent miscarriages. Hum Reprod 26:491–497. doi:10.1093/humrep/deq341

Fazekasova H, Golshayan D, Read J, Tsallios A, Tsang JY, Dorling A, George AJ, Lechler RI, Lombardi G, Mirenda V (2009) Regulation of rat and human T-cell immune response by pharmacologically modified dendritic cells. Transplantation 87:1617–1628. doi:10.1097/TP.0b013e3181a5504c

Fink K, Duval A, Martel A, Soucy-Faulkner A, Grandvaux N (2008) Dual role of NOX2 in respiratory syncytial virus- and Sendai virus-induced activation of NF-kappaB in airway epithelial cells. J Immunol 180:6911–6922

Flajollet S, Poras I, Carosella ED, Moreau P (2009) RREB-1 is a transcriptional repressor of HLA-G. J Immunol 183:6948–6959. doi:10.4049/jimmunol.0902053

Fregonezi PA, Silva TG, Simões RT, Moreau P, Carosella ED, Kläy CP, Gonçalves MA, Soares EG, Souto F, Donadi EA, Soares CP (2010 Oct 29) Expression of nonclassical molecule human leukocyte antigen-G in oral lesions. Am J Otolaryngol. doi:10.1016/j.amjoto.2010.08.001

Fritzsching B, Oberle N, Pauly E, Geffers R, Buer J, Poschl J, Krammer P, Linderkamp O, Suri-Payer E (2006) Naive regulatory T cells: a novel subpopulation defined by resistance toward CD95L-mediated cell death. Blood 108:3371–3378

Gazit E, Sherf M, Balbin E, Muratov A, Goldstein I, Loewenthal R (2007) HLA-G expression is induced in Epstein-Barr virus-transformed B-cell lines by culture conditions. Hum Immunol 68:463–468. doi:10.1016/j.humimm.2007.02.009

Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van Duijnhoven GCF, Middel J, Cornelissen ILMHA, Nottet HSLM, KewalRamani VN, Littman DR, Figdor CG, van Kooyk Y (2000) DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. Cell 100:587–597. doi:10.1016/S0092-8674(00)80694-7

Geng S, Ye JJ, Zhao JL, Li TS, Han Y (2011) Cytomegalovirus retinitis associated with acquired immunodeficiency syndrome. Chin Med J (Engl) 124:1134–1138

Girardi G, Prohászka Z, Bulla R, Tedesco F, Scherjon S (2011) Complement activation in animal and human pregnancies as a model for immunological recognition. Mol Immunol 48:1621–1630. doi:10.1016/j.molimm.2011.04.011

Gonzalez JM, Xu H, Ofori E, Elovitz MA (2007) Toll-like receptors in the uterus, cervix, and placenta: is pregnancy an immunosuppressed state? Am J Obstet Gynecol 197:296.e1–296.e6. doi:10.1016/j.ajog.2007.06.021

Gorczynski RM, Chen Z, Clark DA, Kai Y, Lee L, Nachman J, Wong S, Marsden P (2004) Structural and functional heterogeneity in the CD200R family of immunoregulatory molecules and their expression at the feto-maternal interface. Am J Reprod Immunol 52:147–163. doi:10.1111/j.1600-0897.2004.00192.x

Götherström C, West A, Liden J, Uzunel M, Lahesmaa R, Le Blanc K (2005) Difference in gene expression between human fetal liver and adult bone marrow mesenchymal stem cells. Haematologica 90:1017

Gregori S, Tomasoni D, Pacciani V, Scirpoli M, Battaglia M, Magnani CF, Hauben E, Roncarolo MG (2010) Differentiation of type 1 T regulatory cells (Tr1) by tolerogenic DC-10 requires the IL-10-dependent ILT4/HLA-G pathway. Blood 116:935–944

Guaní-Guerra E, Negrete-García MC, Montes-Vizuet R, Asbun-Bojalil J, Terán LM (2011) Human β-defensin-2 induction in nasal mucosa after administration of bacterial lysates. Arch Med Res 42:189–194

Guilbride DL, Gawlinski P, Guilbride PDL (2010) Why functional pre-erythrocytic and blood-stage malaria vaccines fail: a meta-analysis of fully protective immunizations and novel immunological model. PLoS One 5(5):e10685. doi:10.1371/journal.pone.0010685

Guleria I, Khosroshahi A, Ansari MJ, Habitch A, Azuma M, Yagita H, Noelle RJ, Coyle A, Mellor AL, Khoury SJ, Sayegh MH (2005) A critical role for programmed death ligand 1 in fetal maternal tolerance. J Exp Med 202:231–237. doi:10.1084/jem.20050019

Gupta SR, Phan IT, Suhler EB (2011) Successful treatment of refractory sympathetic ophthalmia in a child with infliximab. Arch Ophthalmol 129:250–252. doi:10.1001/archophthalmol.2010.358

Gutiérrez G, Malan Borel I, Margni RA (2001) The placental regulatory factor involved in the asymmetric IgG antibody synthesis responds to IL-6 features. J Reprod Immunol 49:21–32. doi:10.1016/S0165-0378(00)00074-7

Habicht A, Dada S, Jurewicz M, Fife B, Yagita H, Azuma M, Sayegh M, Guleria I (2007) A link between PDL1 and T regulatory cells in the fetomaternal tolerance. J Immunol 179:5211–5219

Harlap S, Shiono PH (1980) Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. Lancet 2:173–176. doi:10.1016/S0140-6736(80)90061-6

Hedger MP (2011) Immunophysiology and pathology of inflammation in the testis and epididymis. J Androl 32(6):625–640

Hee L, Kirkegaard I, Vogel I, Thorsen P, Skogstrand K, Hougaard DM, Uldbjerg N, Sandager P (2011) Low serum interleukin-17 is associated with preterm delivery. Acta Obstet Gynecol Scand 90:92–96. doi:10.1111/j.1600-0412.2010.01017.x

Heidelberger M, Kendall FE (1935) A quantitative theory of the precipitin reaction: III. the reaction between crystalline egg albumin and its homologous antibody. J Exp Med 62:697–720. doi:10.1084/jem.62.5.697

Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S, Lipford G, Wagner H, Bauer S (2004) Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. Science 303:1526–1529. doi:10.1126/science.1093620

Hermonat PL, Kechelava S, Lowery CL, Korourian S (1998) Trophoblasts are the preferential target for human papilloma virus infection in spontaneously aborted products of conception. Hum Pathol 29:170–174. doi:10.1016/S0046-8177(98)90228-3

Holtan SG, Creedon DJ, Haluska P, Markovic SN (2009) Cancer and pregnancy: parallels in growth, invasion, and immune modulation and implications for cancer therapeutic agents. Mayo Clin Proc 84:985–1000. doi:10.4065/84.11.985, Review

Holtan SG, Creedon DJ, Thompson MA, Nevala WK, Markovic SN (2011) Expansion of CD16-negative natural killer cells in the peripheral blood of patients with metastatic melanoma. Clin Dev Immunol 2011:316314. doi:10.1155/2011/316314

Hong Y, Wang X, Lu P, Song Y, Lin Q (2008) Killer immunoglobulin-like receptor repertoire on uterine natural killer cell subsets in women with recurrent spontaneous abortions. Eur J Obstet Gynecol Reprod Biol 140:218–223. doi:10.1016/j.ejogrb.2008.04.011

Hunger RE, Sieling PA, Ochoa MT, Sugaya M, Burdick AE, Rea TH, Brennan PJ, Belisle JT, Blauvelt A, Porcelli SA, Modlin RL (2004) Langerhans cells utilize CD1a and langerin to efficiently present nonpeptide antigens to T cells. J Clin Invest 113:701–708. doi:10.1172/JCI19655

Ichim TE, Harman RJ, Min WP, Minev B, Solano F, Rodriguez JP, Alexandrescu DT, De Necochea-Campion R, Hu X, Marleau AM, Riordan NH (2010) Autologous stromal vascular fraction cells: a tool for facilitating tolerance in rheumatic disease. Cell Immunol 264:7–17. doi:10.1016/j.cellimm.2010.04.002, Review

Ikegami T, Makino S (2011) The pathogenesis of rift valley fever. Viruses 3:493–519. doi:10.3390/v3050493

Ito K, Tanaka T, Tsutsumi N, Obata F, Kashiwagi N (1999a) Possible mechanisms of immunotherapy for maintaining pregnancy in recurrent spontaneous aborters: analysis of antiidiotypic antibodies directed against autologous T-cell receptors. Hum Reprod 14:650–655. doi:10.1093/humrep/14.3.650

Ito T, Inaba M, Inaba K, Toki J, Sogo S, Iguchi T, Adachi Y, Yamaguchi K, Amakawa R, Valladeau J, Saeland S, Fukuhara S, Ikehara S (1999b) A CD1a+/CD11c + subset of human blood dendritic cells is a direct precursor of Langerhans cells. J Immunol 163:1409–1419

Jalal H, Bahadur G, Knowles W, Jin L, Brink N (2004) Mumps epididymo-orchitis with prolonged detection of virus in semen and the development of anti-sperm antibodies. J Med Virol 73:147–150

Jia CS, Liu JN, Li WB, Ma CM, Lin SZ, Hao Y, Gao XZ, Liu XL, Xu YF, Zhang LF, Qin C (2010) The cross-reactivity of the enterovirus 71 to human brain tissue and identification of the cross-reactivity related fragments. Virol J 7:47. doi:10.1186/1743-422X-7-47

Jiang Y, Zhu J, Xu G, Liu X (2011a) Intranasal delivery of stem cells to the brain. Expert Opin Drug Deliv 8:623–632. doi:10.1517/17425247.2011.566267

Jiang Y, Chen S, Jia S, Zhu Z, Gao X, Dong D, Gao Y (2011b) Association of HLA-G 3′ UTR 14-bp insertion/deletion polymorphism with hepatocellular carcinoma susceptibility in a Chinese population. DNA Cell Biol 30(12):1027–1032

John LJ, Fromm M, Schulzke JD (2011) Epithelial barriers in intestinal inflammation. Antioxid Redox Signal 15:1255–1270. doi:10.1089/ars.2011.3892

Julander JG, Winger QA, Rickords LF, Shi PY, Tilgner M, Binduga-Gajewska I, Sidwell RW, Morrey JD (2006) West Nile virus infection of the placenta. Virology 347:175–182. doi:10.1016/j.virol.2005.11.040

Kammerer R, Zimmermann W (2010) Coevolution of activating and inhibitory receptors within mammalian carcinoembryonic antigen families. BMC Biol 8:12. doi:10.1186/1741-7007-8-12

Kaštelan S, Tomić M, Pavan J, Orešković S (2010) Maternal immune system adaptation to pregnancy–a potential influence on the course of diabetic retinopathy. Reprod Biol Endocrinol 8:124–130

Kawamura T, Kurtz SE, Blauvelt A, Shimada S (2005) The role of Langerhans cells in the sexual transmission of HIV. J Dermatol Sci 40:147–155. doi:10.1016/j.jdermsci.2005.08.009

Keele BF, Estes JD (2011) Barriers to mucosal transmission of immunodeficiency viruses. Blood 118:839–846. doi:10.1182/blood-2010-12-325860

Kelemen K, Bognar I, Paal M, Szekeres-Bartho J (1996) A progesterone-induced protein increases the synthesis of asymmetric antibodies. Cell Immunol 167:129–134. doi:10.1006/cimm.1996.0016

Kelly R, Arnold L, Richards S, Hill A, Bomken C, Hanley J, Loughney A, Beauchamp J, Khursigara G, Rother RP, Chalmers E, Fyfe A, Fitzsimons E, Nakamura R, Gaya A, Risitano AM, Schubert J, Norfolk D, Simpson N, Hillmen P (2010) The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab. Br J Haematol 149:446–450. doi:10.1111/j.1365-2141.2010.08099.x

Keskin DB, Allan DSJ, Rybalov B, Andzelm MM, Stern JNH, Kopcow HD, Koopman LA, Strominger JL (2007) TGFβ promotes conversion of CD16+ peripheral blood NK cells into CD16- NK cells with similarities to decidual NK cells. Proc Natl Acad Sci U S A 104:3378–3383. doi:10.1073/pnas.0611098104

Kesting MR, Stoeckelhuber M, Kuppek A, Hasler R, Rohleder N, Wolff KD, Nieberler M (2012) Human β-defensins and psoriasin/S100A7 expression in salivary glands: anti-oncogenic molecules for potential therapeutic approaches. BioDrugs 26(1):33–42. doi:10.2165/11597570-000000000-00000, 1 Feb 2012

Klein A, Lefebvre P (2007) Three consecutive episodes of acute retinal necrosis due to herpes simplex-1 over twelve years following herpetic encephalitis. Ocul Immunol Inflamm 15:411–413. doi:10.1080/09273940701662510, Review

Klopfleisch R, Teifke JP, Fuchs W, Kopp M, Klupp BG, Mettenleiter TC (2004) Influence of tegument proteins of pseudorabies virus on neuroinvasion and transneuronal spread in the nervous system of adult mice after intranasal inoculation. J Virol 78:2956–2966

Kobayashi K, Miwa H, Yasui M (2010a) Inflammatory mediators weaken the amniotic membrane barrier through disruption of tight junctions. J Physiol 588:4859. doi:10.1113/jphysiol.2010.197764

Kobayashi K, Kadohira I, Tanaka M, Yoshimura Y, Ikeda K, Yasui M (2010b) Expression and distribution of tight junction proteins in human amnion during late pregnancy. Placenta 31:158–162. doi:10.1016/j.placenta.2009.11.014

Koga K, Mor G (2008) Expression and function of Toll-like receptors at the maternal–fetal Interface. Reprod Sci 15:231–242. doi:10.1177/1933719108316391

Koga K, Cardenas I, Aldo P, Abrahams VM, Peng B, Fill S, Romero R, Mor G (2009) Activation of TLR3 in the trophoblast is associated with preterm delivery. Am J Reprod Immunol 61:196–212. doi:10.1111/j.1600-0897.2008.00682.x

Kolte L, Gaardbo JC, Karlsson I, Sørensen AL, Ryder LP, Skogstrand K, Ladelund S, Nielsen SD (2011) Dysregulation of CD4 + CD25 + CD127lowFOXP3+ regulatory T cells in HIV-infected pregnant women. Blood 117:1861–1868

Koskimies AI, Kormano M, Alfthan O (1973) Proteins of the seminiferous tubule fluid in man–evidence for a blood-testis barrier. J Reprod Fertil 32:79–86. doi:10.1530/jrf.0.0320079

Kristóf K, Madách K, Czaller I, Bajtay Z, Erdei A (2009) Mathematical analysis of clinical data reveals a homunculus of bacterial mimotopes protecting from autoimmunity via oral tolerance in human. Mol Immunol 46:1673–1678. doi:10.1016/j.molimm.2009.02.017

Kukkonen K, Kuitunen M, Haahtela T, Korpela R, Poussa T, Savilahti E (2010) High intestinal IgA associates with reduced risk of IgE-associated allergic diseases. Pediatr Allergy Immunol. 21(1 Pt 1):67–73

Kumazaki K, Nakayama M, Yanagihara I, Suehara N, Wada Y (2004) Immunohistochemical distribution of Toll-like receptor 4 in term and preterm human placentas from normal and complicated pregnancy including chorioamnionitis. Hum Pathol 35:47–54. doi:10.1016/j.humpath.2003.08.027

Kuroki K, Maenaka K (2007) Immune modulation of HLA-G dimer in maternal-fetal interface. Eur J Immunol 37:1727–1729. doi:10.1002/eji.200737515, Review

Lafay F, Coulon P, Astic L, Saucier D, Riche D, Holley A, Flamand A (1991) Spread of the CVS strain of rabies virus and of the avirulent mutant AvO1 along the olfactory pathways of the mouse after intranasal inoculation. Virology 183:320–330

Lafon M (2008) Immune evasion, a critical strategy for rabies virus. Dev Biol (Basel) 131:413–419, Review

Landek-Salgado MA, Rose NR, Caturegli P (2011) Placenta suppresses experimental autoimmune hypophysitis through soluble TNF receptor 1. J Autoimmun July 23. doi:10.1016/j.jaut.2011.07.001

Langerhans P (1868) Über die Nerven der menschlichen Haut. Virchows Arch [Pathol Anat] 44:325–337

Lathrop SK, Bloom SM, Rao SM, Nutsch K, Lio CW, Santacruz N, Peterson DA, Stappenbeck TS, Hsieh CS (2011) Peripheral education of the immune system by colonic commensal microbiota. Nature 478(7368):250–254. doi:10.1038/nature10434

Le Bouteiller P, El Costa H, Aguerre-Girr M, Tabiasco J (2009) Immunity of pregnancy: novel concepts. Bull Acad Natl Med 193:1029–1041, French

Le Tortorec A, Dejucq-Rainsford N (2010) Infection of semen-producing organs by HIV and role in virus dissemination. Med Sci (Paris) 26:861–868. doi:10.1051/medsci/20102610861, Review. French

Lea RG, al-Sharekh N, Tulppala M, Critchley HO (1997) The immunolocalization of bcl-2 at the maternal-fetal interface in healthy and failing pregnancies. Hum Reprod 12:153–158. doi:10.1093/humrep/12.1.153

LeBouder F, Khoufache K, Menier C, Mandouri Y, Keffous M, Lejal N, Krawice-Radanne I, Carosella ED, Rouas-Freiss N, Riteau B (2009) Immunosuppressive HLA-G molecule is upregulated in alveolar epithelial cells after influenza A virus infection. Hum Immunol 70:1016–1019. doi:10.1016/j.humimm.2009.07.026

Li H, Nowak-Wegrzyn A, Charlop-Powers Z, Shreffler W, Chehade M, Thomas S, Roda G, Dahan S, Sperber K, Berin MC (2006a) Transcytosis of IgE-antigen complexes by CD23a in human intestinal epithelial cells and its role in food allergy. Gastroenterology 131:47–58. doi:10.1053/j.gastro.2006.03.044

Li J, Melenhorst J, Hensel N et al (2006b) T-cell responses to peptide fragments of the BK virus T antigen: implications for cross-reactivity of immune response to JC virus. J Gen Virol 87:2951–2960. doi:10.1099/vir.0.82094-0

Li C, Houser BL, Nicotra ML, Strominger JL (2009) HLA-G homodimer-induced cytokine secretion through HLA-G receptors on human decidual macrophages and natural killer cells. Proc Natl Acad Sci U S A 106:5767–5772. doi:10.1073/pnas.0901173106

Li K, Fazekasova H, Wang N, Sagoo P, Peng Q, Khamri W, Gomes C, Sacks SH, Lombardi G, Zhou W (2011) Expression of complement components, receptors and regulators by human dendritic cells. Mol Immunol 48:1121–1127. doi:10.1016/j.molimm.2011.02.003

Lim KJ, Odukoya OA, Ajjan RA, Li TC, Weetman AP, Cooke ID (2000) The role of T-helper cytokines in human reproduction. Fertil Steril 73:136–142. doi:10.1016/S0015-0282(99)00457-4

Lin Y, Zhong Y, Saito S, Chen Y, Shen W, Di J, Zeng S (2009) Characterization of natural killer cells in nonobese diabetic/severely compromised immunodeficient mice during pregnancy. Fertil Steril 91:2676–2686. doi:10.1016/j.fertnstert.2007.08.087

Lin WH, Griffin DE, Rota PA, Papania M, Cape SP, Bennett D, Quinn B, Sievers RE, Shermer C, Powell K, Adams RJ, Godin S, Winston S (2011) Successful respiratory immunization with dry powder live-attenuated measles virus vaccine in rhesus macaques. Proc Natl Acad Sci U S A 108:2987–2992. doi:10.1073/pnas.1017334108

Liu YS, Wu L, Tong XH, Wu LM, He GP, Zhou GX, Luo LH, Luan HB (2010) Study on the relationship between Th17 cells and unexplained recurrent spontaneous abortion. Am J Reprod Immunol 65(5):503–511. doi:10.1111/j.1600-0897.2010.00921.x

Logan SK, Hansell EJ, Damsky CH, Werb Z (1996) T-antigen inhibits metalloproteinase expression and invasion in human placental cells transformed with temperature-sensitive simian virus 40. Matrix Biol 15:81–89. doi:10.1016/S0945-053X(96)90149-3

Lopez H, Benard M, Saint-Aubert E, Baron M, Martin H, Al Saati T, Plantavid M, Duga-Neulat I, Berrebi A, Cristini C, Arnaud C, Davrinche C, Davignon JL, Casper C (2011) Novel model of placental tissue explants infected by cytomegalovirus reveals different permissiveness in early and term placentae and inhibition of indoleamine 2,3-dioxygenase activity. Placenta 32:522–530. doi:10.1016/j.placenta

Lopez-Botet M, Bellóna T, Llanoa M, Navarroa F, Garcíaa P, de Miguelet M (2000) Paired inhibitory and triggering NK cell receptors for HLA class I molecules. Hum Immunol 61:7–17. doi:10.1016/S0198-8859(99)00161-5

Lopez-Quintero SV, Ji XY, Antonetti DA, Tarbell JM (2011) A three-pore model describes transport properties of bovine retinal endothelial cells in normal and elevated glucose. Invest Ophthalmol Vis Sci 52:1171–1180. doi:10.1167/iovs.10-5971

Lotz M, Gütle D, Walther S, Ménard S, Bogdan C, Hornef MW (2006) Postnatal acquisition of endotoxin tolerance in intestinal epithelial cells. J Exp Med 203:973–984. doi:10.1084/jem.20050625

Lovy J, Savidant GP, Wright GM (2011) Ontogeny and disease responses of Langerhans-like cells in lymphoid tissues of salmonid fish. Cell Tissue Res 346(1):111–118

Lund J, Sato A, Akira S, Medzhitov R, Iwasaki A (2003) Toll-like receptor 9-mediated recognition of Herpes simplex virus-2 by plasmacytoid dendritic cells. J Exp Med 198:513–520. doi:10.1084/jem.20030162

Lutsenko MT, Dorofienko NN, Andrievskaya IA (2010) Morphofunctional characteristics of syncytiotrophoblast and content of heat shock protein 70 in it during exacerbation of

herpesvirus infection in pregnant women. Bull Exp Biol Med 150:149–152. doi:10.1007/s10517-010-1090-1

Ma Y, Zhang P, Wang F, Yang J, Yang Z, Qin H (2010) The relationship between early embryo development and tumorigenesis. J Cell Mol Med 14(12):2697–2701. doi:10.1111/j.1582-4934.2010.01191.x

Malan Borel I, Gentile T, Angelucci J, Pividori J, Guala MC, Binaghi RA, Margni RA (1991) IgG asymmetric molecules with antipaternal activity isolated from sera and placenta of pregnant human. J Reprod Immunol 20:129–140. doi:10.1016/0165-0378(91)90029-P

Malden MA, Mi S, Lee X, Li X, Veldman GM, Finnerty H, Racie L, LaVallie E, Tang XY, Edouard P, Howes S, Keith JC Jr, McCoy JM (2000) Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. Nature 403:785–789. doi:10.1038/35001608

Marchini G, Lindow S, Brismar H, Ståbi B, Berggren V, Ulfgren AK, Lonne-Rahm S, Agerberth B, Gudmundsson GH (2002) The newborn infant is protected by an innate antimicrobial barrier: peptide antibiotics are present in the skin and vernix caseosa. Br J Dermatol 147:1127–1134. doi:10.1046/j.1365-2133.2002.05014.x

Marco DE, Cannas SA, Montemurro MA, Hu B, Cheng SY (2009) Comparable ecological dynamics underlie early cancer invasion and species dispersal, involving self-organizing processes. J Theor Biol 256:65–75. doi:10.1016/j.jtbi.2008.09.011

Margni RA, Malan Borel I (1998) Paradoxical behavior of asymmetric IgG antibodies. Immunol Rev 163:77–87. doi:10.1111/j.1600-065X.1998.tb01189.x, Review

Margni RA, Borel IM, Kapovic M, Angelucci J, Miranda S, Kinsky R, Chaouat G (1992) The proportion of symmetric and asymmetric IgG antibody molecules synthesized by a cellular clone (hybridoma) can be regulated by placental culture supernatants. Cell Immunol 142:287–295. doi:10.1016/0008-8749(92)90290-6

Martorell M, Gil-Salom M, Pérez-Vallés A, Garcia JA, Rausell N, Senpere A (2005) Presence of human papillomavirus DNA in testicular biopsies from nonobstructive azoospermic men. Arch Pathol Lab Med 129:1132–1136

Mas J-L, Lamy C (1998) Stroke in pregnancy and the postpartum period. In: Ginsberg MD, Bogousslavsky J (eds) Cerebrovascular disease: pathophysiology, diagnosis and management. Blackwell Science, Malden, pp 1684–1697

Masarani M, Wazait H, Dinneen M (2006) Mumps orchitis. J R Soc Med 99:573–575. doi:10.1258/jrsm.99.11.573, Review

Matovina M, Husnjak K, Milutin N, Ciglar S, Grce M (2004) Possible role of bacterial and viral infections in miscarriages. Fertil Steril 81:662–669. doi:10.1016/j.fertnstert.2003.08.020

Mégret F, Prehaud C, Lafage M, Moreau P, Rouas-Freiss N, Carosella ED, Lafon M (2007) Modulation of HLA-G and HLA-E expression in human neuronal cells after rabies virus or herpes virus simplex type 1 infections. Hum Immunol 68:294–302. doi:10.1016/j.humimm.2006.12.003

Mi S, Lee X, Li X, Veldman GM, Finnerty H, Racie L, LaVallie E, Tang XY, Edouard P, Howes S, Keith JC Jr, McCoy JM (2000) Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. Nature. 403(6771):785–789

Miyara M, Amoura Z, Parizot C, Badoual C, Dorgham K, Trad S, Nochy D, Debré P, Piette JC, Gorochov G (2005) Global natural regulatory T cell depletion in active systemic lupus erythematosus. J Immunol 175:8392–8400

Miyara M, Yoshioka Y, Kitoh A, Shima T, Wing K, Niwa A, Parizot C, Taflin C, Heike T, Valeyre D, Mathian A, Nakahata T, Yamaguchi T, Nomura T, Ono M, Amoura Z, Gorochov G, Sakaguchi S (2009) Functional delineation and differentiation dynamics of human CD4+ T cells expressing the FoxP3 transcription factor. Immunity 30:899–911. doi:10.1016/j.immuni.2009.03.019

Moffet A, Loke CYW (2006) Immunology of placentation in eutherian mammals. Nat Rev Immunol 6:584–594. doi:10.1038/nri1897

Moffett-King A (2002) Natural killer cells and pregnancy. Nat Rev Immunol 2:656–663. doi:10.1038/nri886

Morales PJ, Pace JL, Platt JS, Langat DK, Hunt JS (2007) Synthesis of beta(2)-microglobulin-free, disulphide-linked HLA-G5 homodimers in human placental villous cytotrophoblast cells. Immunology 122:179–188

Morandi F, Ferretti E, Bocca P, Prigione I, Raffaghello L, Pistoia V (2010) A novel mechanism of soluble HLA-G mediated immune modulation: downregulation of T cell chemokine receptor expression and impairment of chemotaxis. PLoS One 5:e11763. doi:10.1371/journal.pone.0011763

Moreau P, Contu L, Alba F, Lai S, Simoes R, Orrù S, Carcassi C, Roger M, Rabreau M, Carosella ED (2008) HLA-G gene polymorphism in human placentas: possible association of G*0106 allele with preeclampsia and miscarriage. Biol Reprod 79:459–467. doi:10.1095/biolreprod.108.068874

Moreau P, Flajollet S, Carosella ED (2009) Non-classical transcriptional regulation of HLA-G: an update. J Cell Mol Med 13:2973–2989. doi:10.1111/j.1582-4934.2009.00800.x

Moroz C, Livni E, Segal J (1993) Treatment of recurrent spontaneous abortions by immunization with paternal lymphocytes induces immunosuppression by placentalisoferritin. Am J Reprod Immunol. 30(1):32–36

Mruk DD, Su L, Cheng CY (2011) Emerging role for drug transporters at the blood-testis barrier. Trends Pharmacol Sci 32:99–106. doi:10.1016/j.tips.2010.11.007

Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, Cheroutre H (2007) Reciprocal Th17 and regulatory T cell differentiation mediated by retinoic acid. Science 317:256–260. doi:10.1126/science.1145697

Mucida D, Park Y, Cheroutre H (2009) From the diet to the nucleus: vitamin A and TGF-beta join efforts at the mucosal interface of the intestine. Semin Immunol 21:14–21. doi:10.1016/j.smim.2008.08.001

Murai M, Turovskaya O, Kim G, Madan R, Karp CL, Cheroutre H, Kronenberg M (2009) Interleukin 10 acts on regulatory T cells to maintain expression of the transcription factor Foxp3 and suppressive function in mice with colitis. Nat Immunol 10:1178–1184. doi:10.1038/ni.1791

Muretto P (2008) Immunohistochemical study of dendritic cells in foetal skin and lymph-nodes supporting the hypothesis for the neural crest origin of Langerhans cells. Ital J Anat Embryol 113:237–247

Nagamatsu T, Barrier BF, Schust DJ (2011) The regulation of T-cell cytokine production by ICOS-B7H2 interactions at the human fetomaternal interface. Immunol Cell Biol 89:417–425. doi:10.1038/icb.2010.101

Nakada E, Walley KR, Nakada T, Hu Y, von Dadelszen P, Boyd JH (2009) Toll-like receptor-3 stimulation upregulates sFLT-1 production by trophoblast cells. Placenta 30:774–779. doi:10.1016/j.placenta.2009.07.001

Nakada E, Nakada TA, Walley KR, McConechy M, McLaughlin L, von Dadelszen P, Shozu M, Boyd JH (2011) mRNA induces RANTES production in trophoblast cells via TLR3 only when delivered intracellularly using lipid membrane encapsulation. Placenta 32:500–505. doi:10.1016/j.placenta.2011.04.011

Naumenko VA, Tyulenev YA, Yakovenko SA, Kurilo LF, Shileyko LV, Segal AS, Zavalishina LE, Klimova RR, Tsibizov AS, Alkhovskii SV, Kushch AA (2011) Detection of human cytomegalovirus in motile spermatozoa and spermatogenic cells in testis organotypic culture. Herpesviridae 2:7. doi:10.1186/2042-4280-2-7

Nawaz F, Cicala C, Van Ryk D, Block KE, Jelicic K, McNally JP, Ogundare O, Pascuccio M, Patel N, Wei D, Fauci AS, Arthos J (2011) The genotype of early-transmitting HIV gp120s promotes α (4) β(7)-reactivity, revealing α (4) β(7) +/CD4+ T cells as key targets in mucosal transmission. PLoS Pathog 7:e1001301. doi:10.1371/journal.ppat.1001301

Ness-Schwickerath KJ, Jin C, Morita CT (2010) Cytokine requirements for the differentiation and expansion of IL-17A- and IL-22-producing human Vgamma2Vdelta2 T cells. J Immunol 184:7268–7280

Neutra MR, Mantis NJ, Kraehenbuhl JP (2001) Collaboration of epithelial cells with organized mucosal lymphoid tissues. Nat Immunol 2:1004–1009. doi:10.1038/ni1101-1004

Noorali S, Rotar IC, Lewis C, Pestaner JP, Pace DG, Sison A, Bagasra O (2009) Role of HERV-W syncytin-1 in placentation and maintenance of human pregnancy. Appl Immunohistochem Mol Morphol 17:319–328

Nossal GJV, Pike BL (1975) Evidence for the clonal abortion theory of B-lymphocyte tolerance. J Exp Med 141:904–917

Ogawa Y, Kawamura T, Kimura T, Ito M, Blauvelt A, Shimad S (2009) Gram-positive bacteria enhance HIV-1 susceptibility in Langerhans cells, but not in dendritic cells, via Toll-like receptor activation. Blood 113:5157–5166. doi:10.1182/blood-2008-10-185728

Ohyama M, Fukui T, Tanaka Y, Kato K, Hoshino R, Sugawara T, Yamanaka M, Ijiri R, Sata T, Itani Y (2001) Measles virus infection in the placenta of monozygotic twins. Mod Pathol 14:1300–1303. doi:10.1038/modpathol.3880478

Okazaki T, Honjo T (2006) The PD-1-PD-L pathway in immunological tolerance. Trends Immunol 27:195–201. doi:10.1016/j.it.2006.02.001

Oliveira LH, Fonseca ME, de-Bonis M (1993) Placental phagocyte cells infected with herpes simplex type 2 and echovirus type 19: virological and ultrastuctural aspects. Int J Gynaecol Obstet 42:90. doi:10.1016/0020-7292(93)90487-H

Orgad S, Loewenthal R, Gazit E, Sadetzki S, Novikov I, Carp H (1999) The prognostic value of anti-paternal antibodies and leukocyte immunizations on the proportion of live births in couples with consecutive recurrent miscarriages. Hum Reprod 14:2974–2979. doi:10.1093/humrep/14.12.2974

Pandey MK, Rani R, Agrawal S (2005) An update in recurrent spontaneous abortion. Arch Gynecol Obstet 272:95–108. doi:10.1007/s00404-004-0706-y

Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, Wang Y, Hood L, Zhu Z, Tian Q, Dong C (2005) A distinct lineage of CD4+ T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol 6:1133–1141. doi:10.1038/ni1261

Park B, Spooner E, Houser BL, Strominger JL, Ploegh HL (2010) The HCMV membrane glycoprotein US10 selectively targets HLA-G for degradation. J Exp Med 207:2033–2041. doi:10.1084/jem.20091793

Park SY, Gupta D, Kim CH, Dziarski R (2011) Differential effects of peptidoglycan recognition proteins on experimental atopic and contact dermatitis mediated by treg and th17 cells. PLoS One 6(9):e24961. doi:10.1371/journal.pone.0024961

Parton RG, Richards AA (2003) Lipid rafts and caveolae as portals for endocytosis: new insights and common mechanisms. Traffic 4:724–738. doi:10.1034/j.1600-0854.2003.00128.x

Pasetti MF, Dokmetjian J, Brero ML, Eriksson PV, Ferrero F, Manghi MA (1997) Structure and protective capacity of tetanus and diphtheria antibodies produced during human pregnancy and transferred to new-born. Am J Reprod Immunol 37:250–256

Patni S, Wynen LP, Seager AL, Morgan G, White JO, Thornton CA (2009) Expression and activity of Toll-like receptors 1–9 in the human term placenta and changes associated with labor at term. Biol Reprod 80:243–248. doi:10.1095/biolreprod.108.069252

Pazmany L, Mandelboim O, Vales-Gomez M, David DM, Reyburn HT, Strominger JL (1996) Protection from natural killer cell-mediated lysis by HLA-G expression on target cells. Science 274:792–795. doi:10.1126/science.274.5288.792

Pereira CC, de Freitas LB, de Vargas PR, de Azevedo ML, do Nascimento JP, Spano LC (2010) Molecular detection of adeno-associated virus in cases of spontaneous and intentional human abortion. J Med Virol 82:1689–1693. doi:10.1002/jmv.21841

Petroff MG, Chen L, Philips TA, Azzola D, Sedlmayr P, Hunt JS (2003) B7 family molecules are favourably positioned at the human maternal-fetal interface. Biol Reprod 68:1496–1504

Petroff MG, Kharatyan E, Torry DS, Holets L (2005) The immunomodulatory proteins B7-DC, B7-H2, and B7-H3 are differentially expressed across gestation in the human placenta. Am J Pathol 167:465–473. doi:10.1016/S0002-9440(10)62990-2

Polettini J, Takitane J, Peraçoli JC, Silva MG (2011) Expression of β defensins 1, 3 and 4 in chorioamniotic membranes of preterm pregnancies complicated by chorioamnionitis. Eur J Obstet Gynecol Reprod Biol 157:150–155. doi:10.1016/j.ejogrb.2011.03.014

Polgár B, Kispál G, Lachmann M, Paar C, Nagy E, Csere P, Mikó E, Szereday L, Varga P, Szekeres-Bartho J (2003) Molecular cloning and immunological characterization of a novel cDNA coding for progesteron-induced blocking factor. J Immunol 171:5956–5963

Polifka JE, Friedman JM (1991) Environmental toxins and recurrent pregnancy loss. Infertil Reprod Med Clin North Am 2:175–213

Quick AM, Cipolla MJ (2005) Pregnancy-induced up-regulation of aquaporin-4 protein in brain and its role in eclampsia. FASEB J 19:170–175, Review

Rao RK, Baker RD, Baker SS, Gupta A, Holycross M (1997) Oxidant-induced disruption of intestinal epithelial barrier function: role of protein tyrosine phosphorylation. Am J Physiol 273:G812–G823

Reznikoff-Etievant MF (1988) Abortions of immunologic origin. Reprod Nutr Dev 28(6B): 1615–1627. doi:10.1051/rnd:19881007, Review. French

Riley JK (2008) Trophoblast immune receptors in maternal-fetal tolerance. Immunol Invest 37:395–426. doi:10.1080/08820130802206066, Review

Riley JK, Nelson DM (2010) Toll-like receptors in pregnancy disorders and placental dysfunction. Clin Rev Allergy Immunol 39:185–193. doi:10.1007/s12016-009-8178-2, Review

Riley JK, Yokoyama WM (2008) NK cell tolerance and the maternal-fetal interface. Am J Reprod Immunol 59:371–387. doi:10.1111/j.1600-0897.2008.00593.x, Review

Robertson SA, Guerin LR, Moldenhauer LM, Hayball JD (2009) Activating T regulatory cells for tolerance in early pregnancy – the contribution of seminal fluid. J Reprod Immunol 83:109–116. doi:10.1016/j.jri.2009.08.003

Román A, Rodríguez M, Herraiz MA, Jordá J, Cervera I, Peñaloza J, Vidart JA, Martinez-Laso J (2009) Heterogeneous expression of HLA-G1, -G2, -G5, -G6, and -G7 in myeloid and plasmacytoid dendritic cells isolated from umbilical cord blood. Hum Immunol 70:104–109. doi:10.1016/j.humimm.2008.12.001

Rosseels V, Nazé F, De Craeye S, Francart A, Kalai M, Van Gucht S (2011) A non-invasive intranasal inoculation technique using isoflurane anesthesia to infect the brain of mice with rabies virus. J Virol Methods 173:127–136. doi:10.1016/j.jviromet.2011.01.019

Roulet V, Satie AP, Ruffault A, Le Tortorec A, Denis H, Guist'hau O, Patard JJ, Rioux-Leclerq N, Gicquel J, Jégou B, Dejucq-Rainsford N (2006) Susceptibility of human testis to human immunodeficiency virus-1 infection in situ and in vitro. Am J Pathol 169:2094–2103. doi:10.2353/ajpath.2006.060191

Rubio C, Simon C, Vidal F, Rodrigo L, Pehlivan T, Remohi J, Pellicer A (2003) Chromosomal abnormalities and embryo development in recurrent miscarriage couples. Hum Reprod 18:182–188. doi:10.1093/humrep/deg015

Saha S, Qi J, Wang S, Wang M, Li X, Kim Y-G, Núñez G, Gupta D, Dziarski R (2009) PGLYRP-2 and Nod2 are both required for peptidoglycan-induced arthritis and local inflammation. Cell Host Microbe 5:137–150. doi:10.1016/j.chom.2008.12.010

Saha S, Jing X, Park SY, Wang S, Li X, Guptas D, Dziarski R (2010) Peptidoglycan recognition proteins protect mice from experimental colitis by promoting normal gut flora and preventing induction of interferon-c. Cell Host Microbe 8:147–162. doi:10.1016/j.chom.2010.07.005

Sargent IL, Borzychowski AM, Redman CW (2006) Immunoregulation in normal pregnancy and pre-eclampsia: an overview. Reprod Biomed Online 13:680–686. doi:10.1016/S1472-6483(10)60659-1, Review

Sarkola ME, Grénman SE, Rintala MA, Syrjänen KJ, Syrjänen SM (2008) Human papillomavirus in the placenta and umbilical cord blood. Acta Obstet Gynecol Scand 87:1181–1188. doi:10.1080/00016340802468308

Schneider JJ, Unholzer A, Schaller M, Schafer-Korting M, Korting HC (2005) Human defensins. J Mol Med 83:587–595. doi:10.1007/s00109-005-0657-1

Schumacher A, Wafula PO, Bertoja AZ, Sollwedel A, Thuere C, Wollenberg I, Yagita H, Volk HD, Zenclussen AC (2007) Mechanisms of action of regulatory T cells specific for paternal antigens during pregnancy. Obstet Gynecol 110:1137–1145. doi:10.1097/01.AOG.0000284625.10175.31

Schust DJ, Tortorella D, Ploegh HL (1999) HLA-G and HLA-C at the feto-maternal interface: lessons learned from pathogenic viruses. Semin Cancer Biol 9:37–46. doi:10.1006/scbi.1998.0106, Review

Selmani Z, Naji A, Zidi I, Favier B, Gaiffe E, Obert L, Borg C, Saas P, Tiberghien P, Rouas-Freiss N, Carosella ED, Deschaseaux F (2008) Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4 + CD25highFOXP3+ regulatory T cells. Stem Cells 26:212–222. doi:10.1634/stemcells.2007-0554

Selmani Z, Naji A, Gaiffe E, Obert L, Tiberghien P, Rouas-Freiss N, Carosella ED, Deschaseaux F (2009) HLA-G is a crucial immunosuppressive molecule secreted by adult human mesenchymal stem cells. Transplantation 87(Suppl):S62–S66. doi:10.1097/TP.0b013e3181a2a4b3

Shakhawat A, Shaikly V, Elzatma E, Mavrakos E, Jabeen A, Fernández N (2010) Interaction between HLA-G and monocyte/macrophages in human pregnancy. J Reprod Immunol 85:40–46. doi:10.1016/j.jri.2010.02.004, Review

Shi WW, Lin A, Xu DP, Bao WG, Zhang JG, Chen SY, Li J, Yan WH (2011) Plasma soluble human leukocyte antigen-G expression is a potential clinical biomarker in patients with hepatitis B virus infection. Hum Immunol 72(11):1068–1073. doi:10.1016/j.humimm.2011.06.012

Shieh JT, Bergelson JM (2002) Interaction with decay-accelerating factor facilitates coxsackievirus B infection of polarized epithelial cells. J Virol 76:9474–9480. doi:10.1128/JVI.76.18.9474-9480.2002

Shobu T, Sageshima N, Tokui H, Omura M, Saito K, Nagatsuka Y, Nakanishi M, Hayashi Y, Hatake K, Ishitanie A (2006) The surface expression of HLA-F on decidual trophoblasts increases from mid to term gestation. J Reprod Immunol 72:18–32. doi:10.1016/j.jri.2006.02.001

Shyamala G, Sowmya P, Madhavan HN, Malathi J (2008) Relative efficiency of polymerase chain reaction and enzyme-linked immunosorbant assay in determination of viral etiology in congenital cataract in infants. J Postgrad Med 54:17–20. doi:10.4103/0022-3859.39184

Simões RT, Gonçalves MA, Castelli EC, Júnior CM, Bettini JS, Discorde ML, Duarte G, Quintana SM, Simões AL, Moreau P, Carosella ED, Soares EG, Donadi EA (2009) HLA-G polymorphisms in women with squamous intraepithelial lesions harboring human papillomavirus. Mod Pathol 22:1075–1082. doi:10.1038/modpathol.2009.67

Smith JL (2001) A review of hepatitis E virus. J Food Prot 64:572–586, Review

Soni C, Karande AA (2010) Glycodelin A suppresses the cytolytic activity of CD8+ T lymphocytes. Mol Immunol 47:2458–2466. doi:10.1016/j.molimm.2010.06.008

Soundararajan R, Rao AJ (2004) Trophoblast 'pseudo-tumorigenesis': significance and contributory factors. Reprod Biol Endocrinol 25;2:15. Review

Souto FJ, Crispim JC, Ferreira SC, da Silva AS, Bassi CL, Soares CP, Zucoloto S, Rouas-Freiss N, Moreau P, Martinelli AL, Donadi EA (2011) Liver HLA-G expression is associated with multiple clinical and histopathological forms of chronic hepatitis B virus infection. J Viral Hepat 18:102–105. doi:10.1111/j.1365-2893.2010.01286.x

Stoyanova V, Petrova S, Tchorbadjieva M, Deliyska B, Vasilev V, Tsacheva I (2011) New insight into the autoimmunogenicity of the complement protein C1q. Mol Immunol 48:678–682. doi:10.1016/j.molimm.2010.11.010

Stray-Pedersen B, Stray-Pedersen S (1984) Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol 148:140–146

Sugiura-Ogasawara M, Furukawa TA, Nakano Y, Hori S, Aoki K, Kitamura T (2002) Depression as a potential causal factor in subsequent miscarriage in recurrent spontaneous aborters. Hum Reprod 17:2580–2584. doi:10.1093/humrep/17.10.2580

SundarRaj S, Soni C, Karande AA (2009) Glycodelin A triggers T cell apoptosis through a novel calcium-independent galactose-binding lectin activity. Mol Immunol 46:3411–3419. doi:10.1016/j.molimm.2009.07.013

Suzuki Y, Nakazawa M, Suzuki K, Yamazaki H, Miyagawa Y (2011) Expression profiles of cytokines and chemokines in vitreous fluid in diabetic retinopathy and central retinal vein occlusion. Jpn J Ophthalmol 55:256–263. doi:10.1007/s10384-011-0004-8

Szekeres-Bartho J, Halasz M, Palkovics T (2009) Progesterone in pregnancy; receptor-ligand interaction and signaling pathways. J Reprod Immunol 83:60–64. doi:10.1016/j.jri.2009.06.262

Taglauer ES, Trikhacheva AS, Slusser JG, Petroff MG (2008) Expression and function of PCD1 at the human maternal-fetal interface. Biol Reprod 79:562–569. doi:10.1095/biolreprod.107.066324

Taglauer ES, Yankee TM, Petroff MG (2009) Maternal PD-1 regulates accumulation of fetal antigen-specific CD8+ T cells in pregnancy. J Reprod Immunol 80:12–21. doi:10.1016/j.jri.2008.12.001

Takakuwa K, Adachi H, Hataya I, Ishii K, Tamura M, Tanaka K (2003) Molecular genetic studies of HLA-DRB1 alleles in patients with unexplained recurrent abortion in the Japanese population. Hum Reprod 18:728–733. doi:10.1093/humrep/deg188

Tang Q, Henriksen KJ, Bi M, Finger EB, Szot G, Ye J, Masteller EL, McDevitt H, Bonyhadi M, Bluestone JA (2004) In vitro expanded antigen-specific regulatory T cells suppress autoimmune diabetes. J Exp Med 199:1455–1465. doi:10.1084/jem.20040139

Tao L, Suhua C, Juanjuan C, Zongzhi Y, Juan X, Dandan Z (2011) In vitro study on human cytomegalovirus affecting early pregnancy villous EVT's invasion function. Virol J 8:114. doi:10.1186/1743-422X-8-114

Terayama H, Itoh M, Naito M, Hirai S, Qu N, Kuerban M, Musha M (2011) Experimental model of autoimmune orchitis with abdominal placement of donor's testes, epididymides, and vasa deferentia in recipient mice. J Reprod Immunol 90:195–201. doi:10.1016/j.jri.2011.03.008

Tilburgs T, van der Mast BJ, Nagtzaam NM, Roelen DL, Scherjon SA, Claas FH (2009) Expression of NK cell receptors on decidual T cells in human pregnancy. J Reprod Immunol 80:22–32. doi:10.1016/j.jri.2009.02.004

Tiwari V, Oh MJ, Kovacs M, Shukla SY, Valyi-Nagy T, Shukla D (2008) Role for nectin-1 in herpes simplex virus 1 entry and spread in human retinal pigment epithelial cells. FEBS J 275:5272–5285. doi:10.1111/j.1742-4658.2008.06655.x

Tóth FD, Aboagye-Mathiesen G, Nemes J, Liu X, Andirkó I, Hager H, Zdravkovic M, Szabó J, Kiss J, Aranyosi J, Ebbesen P (1997) Epstein-Barr virus permissively infects human syncytiotrophoblasts in vitro and induces replication of human T cell leukemia-lymphoma virus type I in dually infected cells. Virology 229:400–414. doi:10.1006/viro.1997.8449

Triantafilou M, Gamper FG, Haston RM, Mouratis MA, Morath S, Hartung T, Triantafilou K (2006) Membrane sorting of toll-like receptor (TLR)-2/6 and TLR2/1 heterodimers at the cell surface determines heterotypic associations with CD36 and intracellular targeting. J Biol Chem 281:31002–31011

Trinchieri G, Sher A (2007) Cooperation of Toll-like receptor signals in innate immune defence. Nat Rev Immunol 7:179–190. doi:10.1038/nri2038

van der Vlist M, de Witte L, de Vries RD, Litjens M, de Jong MA, Fluitsma D, de Swart RL, Geijtenbeek TB (2011) Human Langerhans cells capture measles virus through Langerin and present viral antigens to CD4(+) T cells but are incapable of cross-presentation. Eur J Immunol 41:2619–2631. doi:10.1002/eji.201041305

van Esch BC, Schouten B, de Kivit S, Hofman GA, Knippels LM, Willemsen LE, Garssen J (2011) Oral tolerance induction by partially hydrolyzed whey protein in mice is associated with enhanced numbers of Foxp3(+) regulatory T-cells in the mesenteric lymph nodes. Pediatr Allergy Immunol 22(8):820–826. doi:10.1111/j.1399-3038.2011.01205.x

Vandercam T, Hintzen RQ, de Boer JH, Van der Lelij A (2008) Herpetic encephalitis is a risk factor for acute retinal necrosis. Neurology 71:1268–1274. doi:10.1212/01.wnl.0000327615.99124.99

Vargas A, Moreau J, Landry S, LeBellego F, Toufaily C, Rassart E, Lafond J, Barbeau B (2009) Syncytin-2 plays an important role in the fusion of human trophoblast cells. J Mol Biol 392:301–318

Vauloup-Fellous C, Hübschen JM, Abernathy ES, Icenogle J, Gaidot N, Dubreuil P, Parent-du-Châtelet I, Grangeot-Keros L, Muller CP (2010) Phylogenetic analysis of rubella viruses involved in congenital rubella infections in France between 1995 and 2009. J Clin Microbiol 48:2530–2535. doi:10.1128/JCM.00181-10

Veazey RS, Lackner AA (2005) HIV swiftly guts the immune system. Nat Med 11(5):469–470

Veazey RS, Springer MS, Marx PA, Dufour J, Klasse PJ, Moore JP (2005) Protection of macaques from vaginal SHIV challenge by an orally delivered CCR5 inhibitor. Nat Med 11(12):1293–1294

Vidricaire G, Tremblay MJ (2007) A clathrin, caveolae, and dynamin-independent endocytic pathway requiring free membrane cholesterol drives HIV-1 internalization and infection in polarized trophoblastic cells. J Mol Biol 368:1267–1283. doi:10.1016/j.jmb.2007.03.003

Virgintino D, Maiorano E, Errede M, Vimercati A, Greco P, Selvaggi L, Roncali L, Bertossi M (1998) Astroglia-microvessel relationship in the developing human telencephalon. Int J Dev Biol 42:1165–1168

Wafula PO, Teles A, Schumacher A, Pohl K, Yagita H, Volk HD, Zenclussen AC (2009) PD-1 but not CTLA-4 blockage abrogates the protective effect of regulatory T cells in a pregnancy murine model. Am J Reprod Immunol 62:283–292. doi:10.1111/j.1600-0897.2009.00737.x

Wagner N, Lohler J, Kunkel EJ, Ley K, Leung E, Krissansen G, Rajewsky K, Müller W (1996) Critical role for beta7 integrins in formation of the gut-associated lymphoid tissue. Nature 382:366–370. doi:10.1038/382366a0

Wang D, Yu QC, Schröer J, Murphy E, Shenk T (2007) Human cytomegalovirus uses two distinct pathways to enter retinal pigmented epithelial cells. Proc Natl Acad Sci U S A 104:20037–20042. doi:10.1073/pnas.0709704104

Wegienka G, Havstad S, Bobbitt KR, Woodcroft KJ, Zoratti EM, Ownby DR, Cole Johnson C (2011) Within-woman change in regulatory T cells from pregnancy to the postpartum period. J Reprod Immunol 88:58–65

Wegner CC, Jordan JA (2004) Human parvovirus B19 VP2 empty capsids bind to human villous trophoblast cells in vitro via the globoside receptor. Infect Dis Obstet Gynecol 12:69–78. doi:10.1080/10647440400009912

Weng PJ, Fu YM, Ding SX, Xu DP, Lin A, Yan WH (2011) Elevation of plasma soluble human leukocyte antigen-G in patients with chronic hepatitis C virus infection. Hum Immunol 72:406–411. doi:10.1016/j.humimm.2011.02.008

Weng X, Lu S, Zhong M, Liang Z, Shen G, Chen J, Wu X (2009) Allo-restricted CTLs generated by coculturing of PBLs and autologous monocytes loaded with allogeneic peptide/HLA/IgG1-Fc fusion protein. J Leukoc Biol 85(3):574–581. doi:10.1189/jlb.0408242

Wewer C, Seibt A, Wolburg H, Greune L, Schmidt MA, Berger J, Galla HJ, Quitsch U, Schwerk C, Schroten H, Tenenbaum T (2011) Transcellular migration of neutrophil granulocytes through the blood-cerebrospinal fluid barrier after infection with Streptococcus suis. J Neuroinflammation 8:51. http://www.jneuroinflammation.com/content/8/1/51

Wilczyński JR (2006) Immunological analogy between allograft rejection, recurrent abortion and pre-eclampsia - the same basic mechanism? Hum Immunol 67:492–511, Review

Witkin S, Linhares I, Bongiovanni A, Herway C, Skupski D (2011) Unique alterations in infection-induced immune activation during pregnancy. BJOG 118(2):145–153. doi:10.1111/j.1471-0528.2010.02773.x

Wramsby ML, Stien Linder M, Bremme K (2000) Primary habitual abortions are associated with high frequency of factor V Leiden mutation. Fertil Steril 4:987–991. doi:10.1016/S0015-0282(00)01545-4

Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, Peh S, Gu J (2006) Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod 74:410–416. doi:10.1095/biolreprod.105.044776

Yan WH (2011) Human leukocyte antigen-G in cancer: are they clinically relevant? Cancer Lett 311(2):123–130. doi:10.1016/j.canlet.2011.07.019

Yang H, Qiu L, Chen G, Lin Q (2008a) Proportional change of CD4+ CD25 + regulatory T cells in decidua and peripheral blood in unexplained recurrent spontaneous abortion patients. Fertil Steril 89:656–661. doi:10.1016/j.fertnstert.2007.03.037

Yang XO, Chang SH, Park H, Nurieva R, Shah B, Acero L, Wang YH, Schluns KS, Broaddus RR, Zhu Z, Dong C (2008b) Regulation of inflammatory responses by IL-17 F. J Exp Med 205:1063–1075. doi:10.1084/jem.20071978

Yarovinsky F, Zhang D, Andersen JF, Bannenberg GL, Serhan CN, Hayden MS, Hieny S, Sutterwala FS, Flavell RA, Ghosh S, Sher A (2005) TLR11 activation of dendritic cells by a protozoan profilin-like protein. Science 308:1626–1629. doi:10.1126/science.1109893

Yoboua F, Martel A, Duval A, Mukawera E, Grandvaux N (2010) Respiratory syncytial virus-mediated NF-kappa B p65 phosphorylation at serine 536 is dependent on RIG-I, TRAF6, and IKK beta. J Virol 84:7267–7277. doi:10.1128/JVI.00142-10

Yoshida M, Claypool SM, Wagner JS, Mizoguchi E, Mizoguchi A, Roopenian DC, Lencer WI, Blumberg RS (2004) Human neonatal Fc receptor mediates transport of IgG into luminal secretions for delivery of antigens to mucosal dendritic cells. Immunity 20:769–783. doi:10.1016/j.immuni.2004.05.007

You H, Liu Y, Agrawal N, Prasad CK, Edwards JL, Osborne AF, Korourian S, Lowery CL, Hermonat PL (2008) Multiple human papillomavirus types replicate in 3A trophoblasts. Placenta 29:30–38. doi:10.1016/j.placenta.2007.08.005

Younes SA, Csire M, Palyi B, Mikala G, Vályi-Nagy I, Cseh I, Benczik M, Jeney C, Takács T, Simon E, Fülöp V, Berencsi G, Fekete G, Visy M (2007) Endotoxins do not influence transplacental transmission of lymphotropic human herpesviruses and human papillomaviruses into amniotic fluid taken from healthy mothers before parturition in Hungary. Acta Microbiol Immunol Hung 54:279–303. doi:10.1556/AMicr.54.2007.3.4

Younes AS, Csire M, Kapusinszky B, Szomor K, Takács M, Berencsi Gy (2009) Heterogeneous pathways of maternal-fetal transmission of human viruses (review). Pathol Oncol Res 15:451–465. doi:10.1007/s12253-009-9166-9

Zhang L, Zhang W, Shao C, Zhang J, Men K, Shao Z, Yan Y, Xu D (2011) Establishment and characterization of a spontaneously immortalized trophoblast cell line (HPT-8) and its hepatitis B virus-expressing clone. Hum Reprod 26:2146–2156. doi:10.1093/humrep/der153

Zheng SG, Wang JH, Gray JD, Soucier H, Horwitz DA (2004) Natural and induced CD4 + CD25+ cells educate CD4 + CD25- cells to develop suppressive activity: the role of IL-2, TGF-beta, and IL-10. J Immunol 172:5213–5221

Zheng XQ, Zhu F, Shi WW, Lin A, Yan WH (2009) The HLA-G 14 bp insertion/deletion polymorphism is a putative susceptible factor for active human cytomegalovirus infection in children. Tissue Antigens 74:317–321. doi:10.1111/j.1399-0039.2009.01312.x

Zhu XM, Han T, Wang XH, Li YH, Yang HG, Luo YN, Yin GW, Yao YQ (2010) Overexpression of miR-152 leads to reduced expression of human leukocyte antigen-G and increased natural killer cell mediated cytolysis in JEG-3 cells. Am J Obstet Gynecol 202:592.e1–592.e7. doi:10.1016/j.ajog.2010.03.002