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ACTIVATION OF THE INNATE IMMUNE RESPONSE IN CRITICAL ILLNESS

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INTRODUCTION

Recognition molecules, inflammatory cells, and the cytokines they produce are the principle means for host tissues to recognize invading microbes, and to initiate intercellular communication between the innate and acquired immune systems. However, activation of host innate immunity may also occur in the absence of microbial recognition, through expression of internal "danger signals" produced by tissue ischemia and necrosis, or through the release of free radicals. When activation of the innate immune system is severe enough, the host response itself can propel the patient into a systemic inflammatory response syndrome (SIRS), or even multi-system organ failure (MSOF) and shock. Although the majority of patients survive the initial SIRS insult, these patients remain at increased risk of developing secondary or opportunistic infections due to the frequent onset of a compensatory anti-inflammatory response syndrome (CARS). The initial activation of the innate immune response often leads to macrophage deactivation, T-cell anergy, and the rapid apoptotic loss of lymphoid tissues, which all contribute to the development of this CARS syndrome and its associated morbidity and mortality. Initial efforts to treat the septic and critically ill patient with anti-cytokine therapies directed at the SIRS response have been disappointing, and therapeutic efforts to modify the immune response during sepsis syndromes will require a more thorough understanding of the innate and acquired immune responses.

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THE INNATE IMMUNE SYSTEM

The primary characteristics of innate (also called natural, nonspecific, or native) immunity are a limited capacity to distinguish one microbe from another, and its fairly stereotypic nature. The principal components of innate immunity are either physical and chemical barriers, such as epithelial and antimicrobial substances produced at epithelial surfaces or blood proteins, including members of the complement system and other mediators of inflammation (cytokine), as well as neutrophils, macrophage and natural killer cells (phagocytic-mediated immune response) (Fig. 1). Innate immunity provides the early nonspecific host defense against microbes and is an integrated multiorgan system effort by the host not only to combat microbial invasion, but also to decrease tissue injury and cell death, promote recovery of the host, and reduce the likelihood of secondary or opportunistic infections (1).

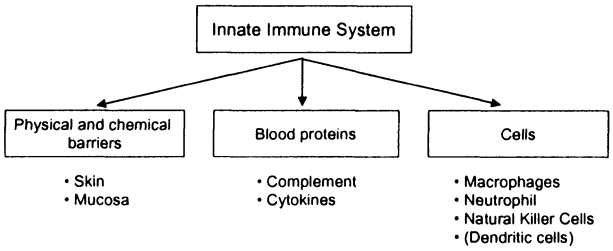

Figure 1: Principal components of innate immune system. Physical and chemical barriers, the complement system, and proinflammatory cytokines, as well as phagocytic and NK cells, are the main components of the innate immune system to protect the human body against microorganism and "danger signals".

ACTIVATION OF THE INNATE IMMUNE SYSTEM AND ITS RESPONSE

Presently, it is recognized that there are two principal mechanisms by which the innate immune system can by activated: either by the presence of invading microorganisms or their products (nonself antigen), or by

endogenous signals of distress or cell damage (self antigen) (Fig. 2). The proposition that the innate immune system relies predominantly on the discrimination between self and nonself entities associated with pathogens has been generally accepted for nearly a decade since its proposition by Charles Janeway (2). More recently, Polly Matzinger has proposed, however, that the innate immune system is less concerned with the differences between self and nonself as it is about its need to protect itself against danger (3). Based on this latter proposal, which has been recently termed the "danger model" (3,4), host innate immunity has also evolved to recognize endogenous signals of distress (for example, the synthesis of heat shock proteins (HSP) or the appearance of nitrosylated proteins or DNA adducts) or cellular damage (necrotic cells/tissues), and therefore does not require foreign or infectious agents for initiation. This latter model can explain the activation of innate immunity and a systemic inflammatory response syndrome to nonmicrobial challenges, such as may occur during ischemia, reperfusion injury, soft tissue injury and hemorrhagic shock.

The early induced but non-adaptive responses to infection or tissue injury is based on non-clonally distributed receptors that recognize certain molecular patterns, also called pathogen-associated molecular patterns, found in microbes, but not in self-tissues (1,5-8). The innate immune system relies primarily on cell-surface receptors, also called pattern recognition receptors and secreted proteins to recognize carbohydrate, but also lipid, protein and DNA structures associated with a microbial infection (Fig. 2). Probably the most well-described cell-surface receptor system for recognition by the innate immune system is the lipopolysaccharide (LPS) recognition complex comprised of CD14 and Toll-like receptor (TLR) family. The Toll-like receptor (TLR) family of cell surface receptors and CD14 function together as a receptor complex for lipopolysaccharides (endotoxins) and possibly some bacterial exotoxins (9,10). The TLR family of receptors and their signaling pathways, however, may play a much larger role in detecting a variety of microbial components and triggering the defensive response. At present, the ligands for only three of the TLR family members are known. Whereas lipopolysaccharide appears to be the principal ligand for TLR4, lipoteichoic acid and peptidoglycans from yeast and Gram positive bacterial pathogens are potential ligands for TLR2 (11-13), and bacterial DNA may be the principal ligand for the TLR9 receptor (14). The innate immune

system, through TLR9, recognizes methylated cytidine phosphate guanosine (CpG) motifs unique to bacterial DNA (15,16) and soluble glycoconjugates (17).

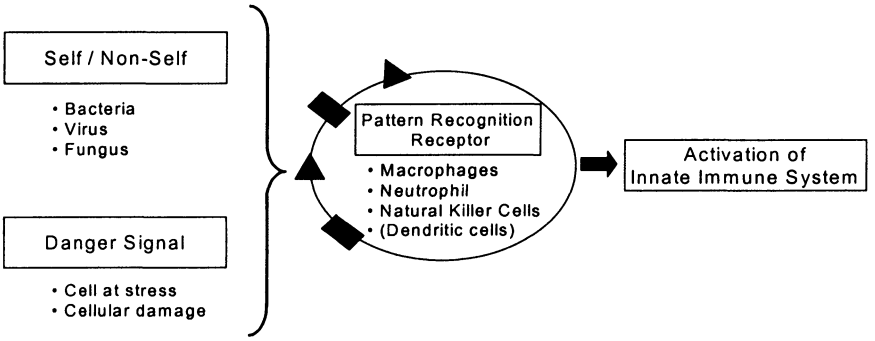

Figure 2. Two different ways to activate the innate immune system. The innate immune system relies cell surface receptors, also called pattern recognition receptors, which can either recognize invading microorganisms (self/non-self) or endogenous signal of distressed or damaged cells (danger signals).

Since the identification of TLR4 as the signal transduction unit for bacterial lipopolysaccharide (18,19), the actual mechanisms by which the innate immune system in mammalian organisms recognize and respond to bacterial lipopolysaccarides have begun to be described. The TLR receptor complexes (TLR2, TLR4 and TLR9) share a common intracellular pathway that ultimately leads to NF-_B activation through signaling via IRAK (IL-1 receptor associated kinase) and MyD88 (20,21). These signaling pathways (IRAK and MyD88) are common to pathways activated by IL-1 signaling through its type I receptor (10). Although these pathways of signaling via TLR4, TLR2, TLR9 and IL-1 share some common components, recent microarray studies from Langer=s laboratory demonstrate that gene expression patterns induced by TLR4, TLR2 and TLR9 agonists in dendritic cells have both common and individual response elements (22).

Probably our best known information concerning activation of innate immunity comes from studies on lipopolysaccharide (LPS) signaling. The interaction between bacterial LPS and the TLR4 receptor is not direct, but involves a required initial binding to other host proteins of the innate immune system, both secretory and membrane associated. Tobias and Ulevitch initially identified a protein from acute phase serum that formed a

stable complex with endotoxin (23) called lipopolysaccharide binding protein or LBP. This 60 kD acute phase protein is synthesized by hepatocytes under regulatory control of proinflammatory cytokines and steroids (24). A major function of LBP is to enable lipopolysaccharide binding to either membrane-associated CD14 or to soluble CD14. LBP appears to have two functional domains, one for binding to lipopolysaccharide and one for binding to the CD14. The primary hypothesis to date is that the lipopolysaccharide:LBP:CD14 complex binds directly to TLR4, which in turn results in a conformational change and transduction of the lipopolysaccharide signal.

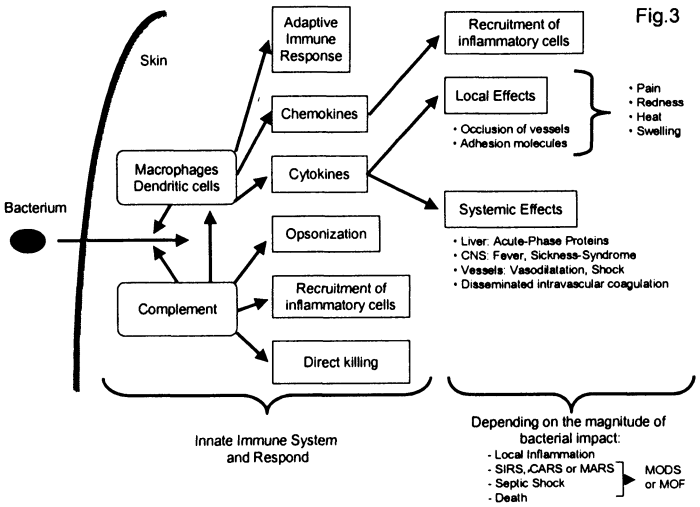

Figure 3: Reaction of the innate immune system against infectious organism. A local non-adaptive response (complement, phagocytes) helps to contain the infection and delivers antigen to local lymph nodes, leading to initiation of adaptive immunity (cell-mediated or humoral), and clearance of the infection. Dependent on the magnitude of the infectious organism to the innate immune system, the response can lead to either a local or a systemic inflammation leading to multiple organ dysfunction syndrome (MODS), multiple organ failure (MOF) or even death.

Innate immunity focused on internal signals as well as exogenous ones has the ability to continuously discriminate between harmful and innocuous signals, as well as between self and nonself, and to generate an immune response only when required. The increasing complexity of the activation of innate immune response assures that it is tightly regulated and finely tuned. The response elements of the innate immune system are triggered by

the release of cytokines, which have three major effects (Fig. 3): first, they induce the production of acute-phase proteins by the liver, which can further bind to bacterial surface molecules and activate complement or phagocytosis. Second, they can elevate body temperature, reduce the host's spontaneous activity, and induce behavioral changes known as "sickness syndrome", which are presumed to be deleterious to the microorganism, while enhancing host antimicrobial functions. Third, they induce local inflammation, in which surface properties and permeability of blood vessels are changed, recruiting phagocytes, immune cells, and molecules to the site of infection.

All these mechanisms have an important role in preventing the systemic dissemination of microbial infection during its early phases while the adaptive (or acquired) immune response is being developed, which will be discussed in an other chapter of this book.

HOW THE INNATE IMMUNE SYSTEM REACTS AGAINST INFECTION

Microorganisms that cause pathology in the humans enter the body at different sites and produce disease by a variety of mechanisms. Such invasion is initially countered by innate defense mechanisms that pre-exist in all individuals and act within seconds of infection (Fig. 1) (1,5-7,25). Body surfaces are defended by epithelia, which provide a physical barrier between the internal milieu and the external world containing pathogens. These surface epithelia are more than a simple physical barrier to infections; they also produce chemical substances that are microbicidal (pH of stomach, digestive enzymes) or inhibit microbial growth (normal flora). Infections occur only when the pathogen can colonize or cross over these barriers.

If microbes are able to successful cross physical barriers, as may occur with simultaneous trauma or tissue injury, alternative complement activation provides a first line of defense (Fig. 3). Complements were discovered many years ago as a heat-labile component of normal plasma that augments the opsonization of bacteria by antibodies and allows some antibodies to kill bacteria. This activity was said to "complement" the antibacterial activity to antibody, hence the name complement. The complement system is made up of a large number of distinct plasma proteins (26). The effector functions of complement can be activated through three pathways. The classical pathway is activated by antibodies (IgG, IgM) binding to antigen. The mannan-

binding lectin pathway (MBLectin pathway) is initiated by binding of serum lectin, the mannan-binding lectin, an acute phase protein secreted by the liver, to mannose-containing carbohydrates on bacteria or virus. Finally, the most important line of defense against microorganisms is the alternative pathway which can be initiated when a spontaneously activated complement (C3) component binds to the surface (C3b) of a pathogen. If C3b binds on the surface of host cells, it is rapidly inactivated by complement regulatory proteins expressed by the host cell, which the bacterial surface does not express: complement receptor 1 (CR1), decay accelerating factor (DAF), and membrane co-factor of proteolysis (MCP) (27). They all generate a crucial enzymatic activity that, in turn, generates the effector molecules of complement. The three main consequences of complement activation are opsonization of pathogen (C3b, C4b), the recruitment of inflammatory cells by anaphylotoxins (C3a, C5a) (28), and direct killing of pathogens (C5b, C6, C7, C8, C9) (Fig. 3) (29).

When pathogens cross the epithelial barrier, they are immediately recognized by phagocytes, which provides innate cellular immunity in tissues, with three important consequences (Fig.3). The first is trapping, engulfment, and destruction of the pathogen by macrophages and migrating neutrophils. The second important effect of the interaction of phagocytes with pathogens and their products is secretion of cytokines by the phagocyte or by dendritic cells (the "professional" antigen presenting cell). There is considerable redundancy in the activation signals recognized by macrophages and dendritic cells to stimulate the release of cytokines. Cytokine release is also induced by the small peptides (anaphylatoxins) released from the complement cascade. And finally, macrophages and dendritic cells act as antigen-presenting cells by presenting engulfed and degraded microorganism peptides on the major histocompatibility complex (MHC) II molecules, and to deliver a co-stimulatory signal through the expression of B7 molecules. Thus, macrophages and dendritic cells are important in the induction of the adaptive immune response, and their released cytokines have an additional role in determining the form of the adaptive immune response (7).

PHYSIOLOGICAL EFFECT OF ACTIVATED INNATE SYSTEM

The activation of complement by the alternative pathway and the engulfment of microorganisms by phagocytosis occur in the early hours of

local infection. To control the local microorganism invasion, additional phagocytic cells and effector molecules like acute-phase proteins are recruited to the site of infection through the release of cytokines and other inflammatory mediators (Fig. 3). The primary cytokines secreted by phagocytes in response to infection are interleukin (IL)-1, IL-6, IL-8 (and other chemokines), IL-12, and tumor necrosis factor (TNF) (30,31). All these cytokines have important local and systemic effects (Fig 3). Moreover, phagocytes release a variety of other molecules in response to infectious agents, including toxic oxygen radicals, peroxides, nitric oxide (NO), and lipid mediators of inflammation such as prostaglandins, leukotrienes - particularly leukotriene B4 (LTB4), and platelet-activating factor (PAF) (32-36).

This local release of inflammatory mediators induces the expression of adhesion molecules on local vessel endothelium cells around the infection site to facilitate the migration of leukocytes out of blood vessels, known as diapedesis, to the infection site. This process involves P-selectin, carried inside endothelial cells in granules known as Weibel-Palade bodies, which appears on endothelial cell surfaces within a few minutes of exposure to leukotriene B4, C5a, or histamine(37,38). A second selectin, E-selectin, appears a few hours after exposure to lipopolysaccharide or TNFa (39-41). The interaction of P-selectin and E-selectin with these surface glycoproteins allows monocytes and neutrophils to adhere reversibly to the vessel wall, so that circulating leukocytes can roll along the endothelium that has been exposed to inflammatory cytokines. Leukocyte integrins like LFA-1 (CD11a:CD18) and CR3 (CD11b:CD18) normally adhere only weakly, but together with IL-8 and other chemoattractant cytokines (chemokines) trigger a conformational change in LFA-1 and CR3 (42). In consequence, the leukocyte attaches firmly to the endothelium and extravasates, and the leukocyte finally migrates along a concentration gradient from chemokines secreted by cells at the site of infection.

Some of the cytokines released in response to infection belong to a family of closely related proteins called chemokines, small polypeptides that are synthesized by phagocytes and many other cells (43-45). All the chemokines function mainly as chemoattractants for leukocytes, monocytes, neutrophils, and other effector cells from the blood to sites infection. Members of chemokine family fall mostly into two broad families: CC chemokines with two adjacent cysteine residues, and CXC chemokines, in which the equivalent two cysteine residues are separated by another amino acid. The two groups of chemokines act on different sets of receptors and different

cell types. In general, the CXC chemokines like IL-8 promote the migration of neutrophils (45), whereas the CC chemokines like macrophage chemoattractant protein-1 (MCP-1) (46) promote the migration of monocytes or other cell types (47,48). The role of chemokines such as IL-8 and MCP-1 in cell recruitment is twofold: first, to convert the initial rolling of the leukocyte on the endothelial cells into stable binding; and second to direct its migration along a concentration gradient that increases in concentration towards the site of infection. This is achieved by the binding of the small, soluble chemokines to proteoglycan molecules in the extracellular matrix and on endothelial cell surface, thus displaying the chemokines on a solid substrate along which the leukocytes can migrate. Once the leukocytes have crossed the vessel endothelium to enter the tissue, their migration to the focus of infection is directed by the gradient of matrix-associated chemokine molecules. Moreover, chemokines can be produced by a wide variety of cells type in response to bacterial products, viruses, and agents that cause physical damage (49-53). Thus, infection or physical damage to tissues sets in motion the recruitment of phagocytic cells to the site of damage. In addition, the activation of complement by infectious agents contributes the inflammatory mediators, C5a and C3a, which are potent inducers of proinflammatory cytokine gene transcription (54). As well as being an inflammatory mediator, C5a is also able to activate mast cells, causing them to release histamine and LTB4, contributing to the changes in endothelial cells at sites of infection (55). The combined local effects of these mediators results in an inflammatory response characterized by pain, redness, heat, and swelling, which usually is one of the immediate local reactions to infection (Fig. 3).

LOCAL AND SYSTEMIC EFFECT OF THE INNATE CYTOKINE TNF

The molecular changes induced at the endothelium cell surface by inflammatory mediators, especially TNF, also induce the expression of molecules on endothelial cells that favor a procoagulant state and trigger blood clotting in the local small vessels, occluding them. This can be important in preventing the pathogen from entering the bloodstream and spreading through the blood to organs all over the body (56-58).

On the other hand, the presence of blood bacteremia is accompanied by the release of TNF by macrophages in the liver, spleen, and other tissue sites.

However, the same mechanisms by which TNF so effectively contains local infection can become catastrophic once the infection spreads to the bloodstream, inducing the systemic release of TNF. The systemic release of TNF, especially when a systemic IL-1 release is also occurring, causes vasodilation and loss of plasma volume leading to increased vascular permeability and ultimately shock. In septic shock, disseminated intravascular coagulation is also triggered by TNF, leading to the fibrin deposition in the small vessels and the massive consumption of clotting proteins (59). Therefore, the individual's ability to clot blood appropriately is lost and the fibrin deposition in the microvasculature leads to ischemic injury in organs and tissues. This condition frequently leads to organ failure, especially in the kidneys, liver, heart, and lungs (60,61) (Fig. 3).

ACTIVATION OF THE ACUTE-PHASE RESPONSE BY INFLAMMATORY OR INNATE CYTOKINES

Cytokines produced by macrophages and neutrophils have long-range effects that contribute to host defense. One of these is the elevation of body temperature, which is generally prostaglandin-dependent and caused by TNF, IL-1, IL-6, and other cytokines. Furthermore, IL-1, IL-6 and TNF activate hepatocytes to produce acute-phase proteins (Fig. 3)(62,63). Of the acute-phase proteins, two are of particular interest because they mimic the action of antibodies but, unlike antibodies, these proteins have broad specificity for pathogen molecules. C-reative protein (CRP) binds to the phosphorylcholine portion of certain bacterial and fungal cell wall lipopolysaccarides (64). When CRP binds to a bacterium, it can not only serve as an opsonin, but can also activate the classical complement cascade. In addition, mannan-binding lectin (MBL) binds to mannose residues, which are accessible on many bacteria, but are covered by other sugar groups in the carbohydrates on vertebrate cells (65). MBL also acts as an opsonin for monocytes and can activate the lectin complement pathway as well (66). Thus, within a day or two, the acute phase response provides the host with two proteins with functional properties of antibodies, and which can bind a broad range of bacteria (64,67). However, unlike antibodies, they have no structural diversity, and are made in response to any stimulus that triggers the release of TNF, IL-1, and IL-6, so their synthesis is not specifically induced and targeted.

NEUTROPHILS ARE THE EARLIEST CELLS TO BE RECRUITED

Neutrophils are abundant in the blood but are absent from normal tissues. They are short-lived, surviving only a few hours after leaving the bone marrow. The innate immune response produces a variety of factors that are chemotactic for neutrophils and they rapidly emigrate from the blood to enter sites of infection. The neutrophils are the earliest phagocytic cells to be recruited (68-70). Later, they are followed by mononuclear cells (Fig. 1). Once in an inflammatory site, the neutrophils are able to eliminate many pathogens by phagocytosis. Neutrophils can either phagocytose antibody-coated pathogens, or microorganisms coated with the complement component C3b. However, neutrophils are able to phagocytose bacteria in the absence of specific antibodies by directly binding of bacterial wall components to several receptors on neutrophils (71,72).

NATURAL KILLER CELLS ARE THE EARLY DEFENSE AGAINST CERTAIN INTRACELLULAR INFECTIONS

Natural killer cells (NK cells) have two types of surface receptor that control their cytotoxic activity. One type triggers killing while the second set of receptors inhibits activation, and prevents NK cells from killing normal cells. These inhibitory receptors are specific for major histocompatibility complex (MHC) class I peptides, which explains why NK cells selectively kill target cells bearing low levels of MHC class I. Thus, one possible mechanism by which NK cells distinguish infected from uninfected cells is by recognizing alterations in MHC class I expression. Another is that they recognize changes in cell-surface glycoproteins induced by viral or bacterial infection (73,74). Moreover NK cells not only play an important role in the innate mechanism of cytotoxic attack, but also play a key role in humoral immunity for destruction of antibody-coated target cells. This antibody-dependent cell mediated cytotoxicity is triggered when antibody bound to the surface of Fc receptors (CD 16) on the NK cells, involving the release of cytoplasmatic granules containing perforin and granyzmes(75,76).

THE ROLE OF INNATE CYTOKINES DURING CRITICAL ILLNESS AND SEPSIS

The principal injurious consequences of host responses to extracellular bacteria are inflammation and septic shock, caused by excessive amounts of proinflammatory cytokines produced mainly by activated macrophages. Septic shock is the most severe cytokine-induced pathologic consequence of infection by bacteria. It is a syndrome characterized by circulatory collapse, metabolic disturbances (hypoglycemia), and disseminated intravascular coagulation. Overproduction of TNF and IL-1 are the principal mediators for septic shock, although IFN-, IL-12 and IL-18 probably contribute significantly. In fact, serum levels of TNF have been shown in some studies to be predictive of the outcome of severe Gram negative bacterial infections (77), although this is by no means a universal observation. Furthermore, some studies have demonstrated a correlation between the magnitude of plasma IL-1, IL-6 and TNF levels with outcome of septic and burn patients(78,79). Interestingly, more recent studies showed that not only proinflammatory cytokines correlated with an adverse outcome, but also anti-inflammatory mediators, such as IL-10, correlated with the severity of trauma patients and an increased risk of developing complications (adult respiratory distress syndrome and sepsis) (80,81). Unfortunately, too much emphasis has been placed on measuring the concentrations of cytokines in the plasma of patients with sepsis syndromes. Although correlations have been frequently seen between elevated concentrations of TNF, IL-1 and other cytokines, and an adverse outcome, the absence of detectable cytokines in the plasma concentration is not indicative of a lack of expression. Several of these cytokines, including TNF and IL-1, can exist in membrane associated forms, and their concentrations at the site of infection are frequently higher than they are in the systemic circulation (82,83)

The immunological cascade resulting in the sepsis responses can be initiated by tissue injury, ischemia-reperfusion injury, Gram-positive organisms and fungi, Gram-negative organisms and their constituent endotoxin. In multiple trauma or hemorrhagic shock, the direct tissue or secondary ischemia-reperfusion injury may lead to cytokine production from endogenous danger signals, or from the increased appearance of microorganisms and exotoxins from the gut. The host response to these microbial products, or trauma and ischemia-reperfusion injury itself, leads to the rapid activation of the innate immune response, and the release of a variety of humoral mediators, including glucocorticoids, catecholamines and

proximal proinflammatory cytokines like TNF, IL-1, IL-6 and chemokines (1)

A vigorous induction of the innate immune system can and often does have catastrophic effects on the patient with sepsis syndrome. Exaggerated production of proinflammatory cytokines and the induction of more distal mediators such as nitric oxide, platelet activation factor and prostaglandins have been implicated in the endothelial changes and induction of a pro-coagulant state that leads to hypotension, inadequate organ perfusion and necrotic cell death associated with MODS (58).

This proinflammatory state has been defined as being the systemic inflammatory response syndrome (SIRS) (84). However, a large majority of these patients survive this initial SIRS event, and the proinflammatory state ultimately resolves. The proinflammatory cytokines and humoral mediators responsible for the induction of the innate immune response and SIRS, also contribute to the development of acquired or specific immune defects. The patient frequently enters an immunological state characterized by T-cell hyporesponsiveness, anergy and a defect in antigen presentation called compensatory anti-inflammatory response syndrome (CARS)(85,86). CARS is characterized by defects in antigen presentation, macrophage "paralysis", T-cell anergy, suppressed T-cell proliferation, decreased T_{H1} cell proliferation and an increase in T-cell and B-cell apoptosis(86).

Exaggerated proinflammatory cytokine production alone does not lead inexorably to an adverse outcome. Complement activation, which is essential in the normal immune response (87) can be detrimental when extensive, since blocking a C5a response protects against lethality (88,89). Similarly, adhesion molecules seem to play an important role in the pathogenesis of sepsis. Patients with septic shock who were treated with antibodies against E-selectin showed signs of resolved shock (90). Counter-regulating E-selectin expression might be one of the therapeutic targets in reducing tissue injury as levels are related to the degree of hemodynamic compromise in critical illness (91). Similarly, administration of anti-L-selectin antibodies have beneficial effects during hemorrhagic shock (92). However, inhibition of adhesion molecules may be molecule specific, as antibodies to P-selectin do not seem to prevent neutrophil-induced liver injury during endotoxic shock (93).

Over-production of proinflammatory cytokines, such as TNFa and IL-1 has been shown to be critical in the development of septic shock (61,94,95), but

clinical trials with inhibitors of proinflammatry cytokines, such as IL-1ra and TNF receptor immunoadhesins and antibodies, have in general failed to improve outcome in septic patients (96,97). There is growing recognition, however, that a large number of patients with sepsis syndrome do not sustain this exaggerated proinflammatory cytokine or SIRS response, but rather, manifest anergy and immune suppression (98). Moreover recent studies have suggested that increased apoptosis of lomphoid organs and some parenchymal tissues may contribute to the immune suppression, anergy and organ system dysfunction. Lymphocyte apoptosis can be induced by several mediators produced during sepsis syndromes, including glucocorticoids and pro-inflammatory cytokines such as TNFa,and Fas ligand (FasL) (99,100). While lymphoid cells are undergoing accelerate apoptosis, spontaneous neutrophil apoptosis associated with sepsis or SIRS is delayed (101,102). This decreased apoptosis is thought to be important in enhancing tissue injury in acute respiratory distress syndrome (ARDS), SIRS and burned injury by promoting a dysbalanced tissue load of neutrophils and uncontrolled release of toxic metabolites injurious to endothelial cells' mitochondria and collagen (Fig. 5) (101,103).

CONCLUSIONS

Progress in treating the critically ill patient with sepsis syndrome requires an improved understanding of its pathogenesis. The introduction of the new terminology such as SIRS, CARS and MARS, has defined critically ill and septic patient's immunological status more clearly. A better understanding of the activated innate immunity and it's physiological response will help to develop new therapeutically approaches. Clearly, new approaches for the treatment of patients with sepsis must be aimed at the immunological abnormalities present. The successful treatment of critical ill and septic patients will likely require multi-modal therapies aimed at several of the immunological and physiological disturbances which are occurring simultaneously.

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