Pathogenesis of Sepsis

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3.1 Introduction

Before the turn of the century, the pathogenesis of sepsis was considered to be driven by an abundant inflammatory response following the invasion of pathogens [1]. Current consensus acknowledges the occurrence of two opposite host reactions to severe infection with proinflammatory and anti-inflammatory features [2]. In sepsis, the normally careful inflammatory balance is disturbed, and hyperinflammation together with immune suppression ensue. This dysregulated immune response to infection is associated with a failure to return to homeostasis and harms the host, resulting in the life-threatening condition called sepsis [3]. While insights in the pathogenesis of sepsis have rapidly grown, this complex syndrome is not yet fully understood, and our increased understanding of pathophysiological mechanisms underlying sepsis has thus far failed to improve health outcome. This chapter provides a brief overview of the pathogenesis of sepsis (Fig. 3.1).

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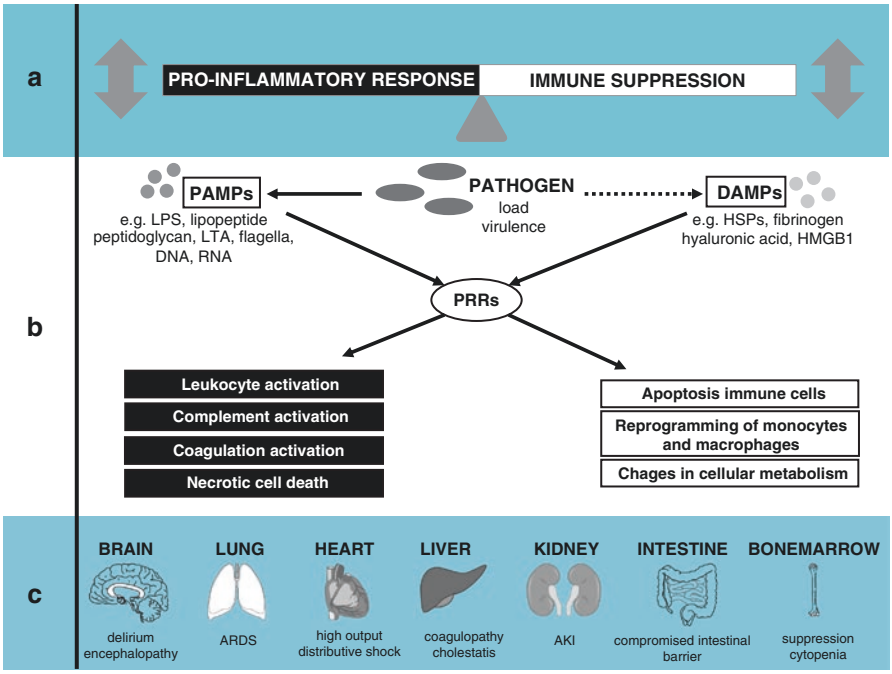

Fig. 3.1 Pathogenesis of sepsis. (**a**) Sepsis is defined as a dysregulated host response to infection, leading to life-threatening organ dysfunction. The normally careful inflammatory balance is disturbed, and this dysregulation is associated with a failure to return to homeostasis. Hyperinflammation and immune suppression ensue, to an extent that is detrimental to the host. (**b**) Once a pathogen has succeeded to cross the mucosal barrier of the host, it can cause sepsis depending on its load and virulence. The host defense system can recognize molecular components of invading pathogens (PAMPs) with specialized receptors (PRRs). Stimulation of PRRs has proinflammatory and immune suppressive consequences. It leads to activation of target genes coding for proinflammatory cytokines (leukocyte activation), inefficient use of the complement system, activation of the coagulation system, and concurrent downregulation of anticoagulant mechanisms and necrotic cell death. This starts a vicious cycle with further progression to sepsis, due to the release of endogenous molecules by injured cells (DAMPs or alarmins), which can further stimulate PRRs. Immune suppression is characterized by massive apoptosis and thereby depletion of immune cells, reprogramming of monocytes and macrophages to a state of a decreased capacity to release proinflammatory cytokines and a disturbed balance in cellular metabolic processes. (**c**) Sepsis is by definition a disease with organ failure. The clinical manifestation can be heterogeneous. Clinicians use physical examination, laboratory testing, and imaging techniques to determine the severity and origin of organ failure. Antimicrobial treatment is aimed to eliminate the causative pathogen, where supportive care is aimed to restore organ function. *ARDS* acute respiratory distress syndrome, *AKI* acute kidney injury, *DAMPs* danger-associated molecular patterns, *DNA* deoxyribonucleic acid, *HMGB1* high-mobility group box-1 protein, *HSPs* heat shock proteins, *LPS* lipopolysaccharide, *LTA* lipoteichoic acid, *PAMPs* pathogen-associated molecular patterns, *PPRs* pattern recognition receptors, *RNA* ribonucleic acid

3.2 Pathogens and Infection Sites

A successful pathogen must attach to and cross the mucosal barrier, escape the host defense system, and multiply to ensure its own survival. All invading microorganisms with a sufficient load and virulence can cause sepsis. However, several

pathogens are well known for their impressive arsenal to attack the host. In a point-prevalence study entailing 14,000 intensive care unit (ICU) patients in 75 countries, 62% of positive isolates were gram-negative bacteria, versus 47% gram-positive and 19% fungal [4]. The most common gram-negative isolates in sepsis patients are *Escherichia coli*, *Klebsiella* sp., and *Pseudomonas aeruginosa*; the most frequent gram-positive organisms are *Staphylococcus aureus* and *Streptococcus pneumoniae* [5, 6]. The incidence of fungal infections as the cause of sepsis is rising, which is problematic due to the associated increased mortality. The most common site of infection is the respiratory tract with 63.5% of the culture-positive infections in the ICU, followed by abdominal infections (19.6%), bloodstream infections (15.1%), renal or urinary tract infections (14.3%), skin infections (6.6%), catheter-related infections (4.7%), infections of the central nervous system (2.9%), and others [4].

3.3 Host Recognition of Pathogens

The host can recognize molecular components of invading pathogens, called pathogen-associated molecular patterns (PAMPs), with specific receptors. Examples of key bacterial PAMPs are lipopolysaccharide (LPS, also known as endotoxin, a cell wall component of gram-negative bacteria), peptidoglycan, lipopeptides (constituents of many pathogens), lipoteichoic acid (a cell wall component of gram-positive bacteria), flagellin (factor in the mobility of bacteria), and bacterial DNA [7]. In the early response to infection, pathogens or more specifically PAMPs are recognized by a limited number of specialized host receptors, known as pattern recognition receptors (PRRs). PRR-mediated pathogen recognition is an important defense mechanism of the host against invading pathogens and results in upregulation of inflammatory gene transcription and initiation of innate immunity [2, 7, 8]. However, if the innate immune system fails to eradicate the pathogen, overstimulation of PRRs by a growing bacterial load can result in dysregulation of the host response, which then no longer benefits the host but causes tissue injury, organ dysfunction, and progression to sepsis. A contributing factor herein is that PRRs can also be stimulated by endogenous molecules released by injured cells, so-called danger-associated molecular patterns (DAMPs or alarmins) [9]. Examples of DAMPs are heat shock proteins, fibrinogen, hyaluronic acid, and high-mobility group box-1 protein (HMGB-1) [9]. Thus, PRRs recognize molecular components of both the pathogen (PAMPs) and the host (DAMPs), resulting in a vicious cycle and perpetuation of inflammation. Four main PRR families have been identified: Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and NOD-like receptors (NLRs) [7, 8].

TLRs comprise the most well-known family of PRRs [7]. They are expressed both extracellularly (TLR1, 2, 4, 5, 6) and intracellularly (TLR3, 7, 8, 9, 10, 11, 12, 13) in endosomes and lysosomes. Ten different TLRs have so far been identified in humans (TLR1–10); 12 are found in mice (TRL1–9, TLR11, TLR12, TLR13) [10]. TLRs are activated by a broad range of ligands presented by bacteria, viruses, parasites, fungi, and the host itself. The signaling pathways of TLRs run via four adaptor proteins, namely, myeloid differentiation primary response

protein 88 (MyD88), TIR domain-containing adaptor protein (TIRAP), TIR domain-containing adaptor protein-inducing IFN-β (TRIF), and TRIF-related adaptor molecule (TRAM). This signaling eventually leads to the translocation of nuclear factor (NF-κB) into the nucleus which starts the transcoding of genes and is crucial for early activation of the immune system [8]. As an example of TLR signaling, TLR4 is stimulated through its ligand LPS, the virulence factor of gram-negative bacteria. It activates both the MyD88- and the TIRAP-dependent pathways for early-phase activation of NF-κB and results in late-phase activation of NF-κB via the TRIF-dependent pathway [7]. TLR3 is stimulated by dsRNA derived from viruses or virus-infected cells and activates the TRIF-dependent pathway [8].

NLRs are cytoplasmic proteins composed of a central nucleotide-binding domain and C-terminal leucine-rich repeats [11]. NLRs are an important factor in the initial immune response through their formation of multiprotein complexes called "inflammasomes." These complexes activate caspase-1 leading to the maturation of proinflammatory cytokines interleukin 1β (IL-1β) and IL-18 [12]. RLRs are cytoplasmic proteins that can recognize the genomic RNA of RNA viruses [13, 14]. CLRs are transmembrane receptors with a carbohydrate-binding domain. CLR-mediated microbial recognition occurs through their ability to recognize carbohydrates on viruses, bacteria, and fungi (Table 3.1).

Table 3.1 Pattern recognition receptors and their ligands in humans

Pattern recognition receptor	Ligand	Origin of ligand
Toll-like receptors (TLRs)		
TLR1	Triacyl lipoprotein (forms heterodimer with TLR2), soluble factors	Bacteria
TLR2	Lipoprotein (forms heterodimer with TLR1 and TLR6)	Bacteria, viruses, fungi, self
TLR3	Double-stranded RNA	Viruses
TLR4	Lipopolysaccharide, envelop proteins (syncytial viruses), glycoinositol phospholipids, HSPs 60 and 70, S100a8 (ligand from dying cells)	Bacteria, viruses, self
TLR5	Flagellin	Bacteria
TLR6	Diacyl lipoprotein (forms heterodimer with TLR2)	Bacteria, viruses
TLR7	Single-stranded RNA, synthetic compounds (e.g., imidazoquinolines)	Bacteria, viruses, self
TLR8	Single-stranded RNA, small purine analog compounds (imidazoquinolines)	Viruses
TLR9	CpG-DNA, insoluble crystal hemozoin (*Plasmodium falciparum*)	Bacteria, viruses, parasites, self
TLR10	Unknown	
NOD-like receptors (NLRs)		
NOD1	Peptidoglycan (iE-DAP)	Bacteria
NOD2	Peptidoglycan (MDP)	Bacteria

Table 3.1 (continued)

Pattern recognition receptor	Ligand	Origin of ligand
C-type lectins (CLRs)		
Dectin-1	β-Glucan	Fungi
Dectin-2	β-Glucan	Fungi
MINCLE	SAP130	Fungi, self
Retinoic acid-inducible gene (RIG)-I-like receptors (RLRs)		
RIG-I	Short double-stranded RNA, 5′triphosphate dsRNA	Viruses
MDA5	Long double-stranded RNA	Viruses
LGP2	Double-stranded RNA	Viruses
DDX3	Viral RNA	Viruses

The innate immune system recognizes pathogens by four main classes of pattern recognition receptors. The table shows the main receptors, their main ligands, and the origin of these ligands. Note that some receptors also recognize "self" antigens, primarily in the context of injury, wherein self-antigens function as alarmins to the host

CpG-DNA cytosine-phosphate-guanosine-DNA, *DDX3* DEAD/H Box 3, *iE-DAP* g-D-glutamyl-meso-diaminopimelic acid, *LGP2* laboratory of genetics and physiology-2, *MDA5* melanoma differentiation-associated gene 5, *MDP* muramyl dipeptide, *MINCLE* macrophage-inducible C-type lectin, *SAP130* Sin3A-associated protein of 130 kDa

Table adapted from Refs. [8, 10, 59]

3.4 Hyperinflammation

Sepsis is associated with a strong activation of the immune system, by stimulation of PRRs by PAMPs and DAMPs, leading to the activation of target genes coding for proinflammatory cytokines such as tumor necrosis factor (TNF), IL-1β, IL-12, and IL-18 [2]. Cytokines are small proteins that can regulate the host response both locally and systemically, after their release from various cell types such as monocytes and neutrophils. These cells can further attribute to activation of the immune system by expression of the triggering receptor expressed on myeloid cells-1 (TREM-1) that amplifies TLR- and NLR-mediated inflammatory response [15]. Several mechanisms regulate the activation of PRRs to avoid overstimulation, including the negative regulators MyD88 short (MyD88s), ST2, single-immunoglobulin interleukin (IL)-1 receptor-related molecule (SIGIRR), toll-interacting protein (TOLLIP), suppressor of cytokine signaling (SOCS), A20, and IRAK-M [16]. If the delicate balance between activation and inhibition of the inflammatory response is disturbed, the pleiotropic hyperinflammatory response in sepsis ensues. This includes activation of the complement and coagulation systems and disturbance of vascular permeability [2], which have been considered important factors in sepsis mortality.

3.4.1 Complement System

The complement system comprises over 40 components that, when activated, work as a cascade and contribute to the innate immune surveillance system [17, 18]. A close collaboration between the complement system and other proinflammatory

stimuli such as cytokines is necessary: the complement system tags dangerous cells or pathogens, and phagocytic cells can respond more properly after activation by proinflammatory mediators. This teamwork is dysregulated in sepsis resulting in inefficient use of the complement system. The complement system contributes directly to the activation of the immune system by the release of anaphylatoxins C3a and C5a. Anaphylatoxins are proinflammatory molecules that activate surrounding cells when they reach a threshold concentration, can lead to the recruitment of other immune cells (macrophages, basophils, neutrophils, eosinophils, and mast cells), and can activate endothelial and epithelial cells and platelets [17, 18]. The harmful role of C5a in sepsis has been linked to neutrophil dysfunction, apoptosis of lymphoid cells, exacerbation of systemic inflammation, cardiomyopathy, disseminated intravascular coagulation (DIC), and complications associated with multiple organ failure [19]. Several experimental sepsis studies have highlighted the beneficial effect of blockage of C5a signaling on outcome [20]. As such, C5a is considered a potential therapeutic target in sepsis.

3.4.2 Coagulation System and Vascular Endothelium

Activation of PRRs leads to upregulation of inflammatory mediators which results in a systemic inflammatory response, including activation of the coagulation system and concurrent downregulation of anticoagulant mechanisms [21]. Coagulation abnormalities can range from mild to clinically relevant fulminant coagulopathies. DIC is the most severe manifestation of disturbed hemostasis with microvascular thrombosis and, through consumption of clotting factors and platelets, simultaneous hemorrhage [22]. The most important initiator of coagulation in sepsis is tissue factor (TF). Indeed, inhibition of TF prevents DIC and improves survival in experimental sepsis [21]. TF is predominantly produced by macrophages and monocytes, and its expression is enhanced by proinflammatory cytokines, exemplifying the close interaction between inflammation and coagulation [23]. Furthermore, TF can reside in micro particles that are formed by hematopoietic and endothelial cells. These micro particles play a significant role in both coagulation and inflammation [24].

In healthy hosts, coagulation is controlled by three main anticoagulant pathways: the antithrombin system, tissue factor pathway inhibitor (TFPI), and the protein C system. In septic patients all these pathways are impaired in their function, partially due to endothelial dysfunction, resulting in low levels of these coagulation inhibitors [25, 26]. The physiological function of the protein C system has been supported by investigations in which interventions inhibiting this pathway resulted in severe coagulopathy and death in otherwise nonlethal infection models. During the early stages of inflammation, plasminogen activators are released to help break down fibrin. Sepsis is associated with high levels of plasminogen activator inhibitor type 1 (PAI-1), a main inhibitor of fibrinolysis, further facilitating microvascular thrombosis [27].

The interaction between inflammation and coagulation is not unilateral. Coagulation factors regulate inflammation in particular through proteolytic cleavage

of protease-activated receptors (PARs) [28]. Activated protein C (APC) influences inflammation, by reducing the expression of receptors for cytokines and chemokines [29], by downregulating the production of inflammatory mediators [30, 31], and by blockage of cytokine release and leukocyte activation [32].

During sepsis the vascular endothelium is involved in the disturbance of anticoagulant mechanisms. Glycosaminoglycans on the endothelial surface support antithrombin-mediated inhibition of thrombin formation and platelet adhesion. Sepsis reduces the production of glycosaminoglycans averting not only antithrombin function but also that of TFPI with regard to inhibiting the main coagulation TF-factor VIIa complex. In healthy hosts endothelium generates APC from protein C through an interaction between thrombin and thrombomodulin (a receptor expressed by endothelial cells); formation of APC by the thrombomodulin-thrombin complex is accelerated by the endothelial protein C receptor (EPCR). APC inactivates coagulation cofactors Va and VIIIa by proteolysis, thereby inhibiting coagulation. In sepsis APC levels are reduced due to impaired production caused by downregulation of both thrombomodulin and EPCR on endothelial cells, as well as by increased consumption.

Adhesion of cells to the endothelium is increased in sepsis. Physiologically, injured endothelium activates von Willebrand factor which forms multimers at the site of injury as a primary step in protective coagulation [25]. Von Willebrand multimers are cleaved by a proteolytic enzyme ADAMTS13 to control adhesion and prevent formation of large obstructive von Willebrand multimers. In sepsis there is a relative deficiency of ADAMTS13 leading to ultra-large von Willebrand multimers at injured sites, contributing to overwhelming platelet adhesion and microvascular thrombosis and possibly eventually multiple organ dysfunction. Furthermore, activation of platelets because of vascular injury during sepsis starts a vicious cycle which leads to more activated endothelium and platelets which further increases coagulation [25].

Impaired vascular barrier function is a key pathogenic mechanism in sepsis, associated with protein leakage into the extravascular space, tissue edema, and diminished microvascular perfusion [25]. Important regulators of vascular barrier function are sphingosine-1-phosphate (S1P) and angiopoietin-1 [25, 33]. S1P activates the endothelial S1P receptor 1, thereby preserving vascular integrity [33]. Angiopoietin-1 activates TIE2, supporting barrier function. Angiopoietin-2 antagonizes angiopoietin-1, and a high angiopoietin-2/angiopoietin-1 ratio has been used as a marker for vascular barrier dysfunction in patients with sepsis [34].

3.4.3 Neutrophil Extracellular Traps

Activation of the coagulation system and vascular injury are amplified by the release of neutrophil extracellular traps (NETs) by neutrophils [35]. NETs are composed of DNA, histones, and neutrophil-derived proteinases and can protect the host by eliminating pathogens. However, NETs may also contribute to collateral damage and thrombosis in the dysregulated immune response in sepsis [35].

3.5 Immune Suppression

Much attention has been drawn to immune suppression in patients with sepsis, which in many patients can already be detected on admission to the ICU and is a prominent feature in those patients that remain in the ICU for extended periods of time [2, 36]. Targeted immune-enhancing therapy may be beneficial for selected patients with immune suppression [2, 36].

Transcriptomic analysis of peripheral blood leucocytes of septic patients recently resulted in the classifications of distinct sepsis endotypes with implications for main pathophysiological mechanisms and prognosis [37, 38]. These studies further confirmed the existence of subgroups of sepsis patients with a predominant immune suppressive phenotype [37, 38].

3.5.1 Apoptosis of Immune Cells

Sepsis-associated immune suppression involves several cell types. During sepsis massive apoptosis leads to depletion of immune cells, especially CD4+ and CD8+ T cells and B cells. This depletion is seen in lymphoid organs and body sites, such as the spleen, thymus, lymph nodes, and gut-associated lymphoid tissue [36, 39]. T regulatory (Treg) cells are more resistant to sepsis-induced apoptosis which, combined with the substantial apoptosis of CD4+ and CD8+ T cells and B cells, lead to a more immune suppressive phenotype. Furthermore, surviving CD4+ and CD8+ T cells shift from a Th1 proinflammatory phenotype to the more immune suppressive Th2 phenotype. Inhibition of lymphocyte apoptosis was associated with better outcomes in various experimental sepsis models, suggesting a causal relationship between lymphocyte apoptosis and sepsis mortality [2, 36]. A recently identified potential therapeutic target in sepsis is the programmed cell death 1 (PD1)–PD1 ligand (PDL1) pathway. Patients with sepsis showed enhanced expression of PD1 on CD4+ T cells together with increased expression of PDL1 on macrophages and endothelial cells [39]. Enhanced PD1–PDL1 interaction is expected to impair T-cell function, and in mice inhibition of this pathway conferred protection against lethality following experimentally induced sepsis [40]. Clinical trials seeking to inhibit PD1–PDL1 signaling in sepsis patients are under way.

Contrary to lymphocytes, apoptosis of neutrophils in sepsis is delayed [2, 36]. Furthermore, the bone marrow releases immature neutrophils which together result in high numbers of circulating neutrophils in different stages of maturation. The function of neutrophils is impaired in sepsis, with reduced chemotaxis and reactive oxygen production.

3.5.2 Reprogramming of Monocytes and Macrophages

Sepsis is further characterized by profound changes in the function of antigen presenting cells [2, 36]. Monocytes and macrophages demonstrate a strongly decreased

capacity to release proinflammatory cytokines upon stimulation with bacterial agonists (a feature commonly referred to as "endotoxin tolerance") and reduced HLA-DR expression. Notably, monocytes/macrophages do not show a general unresponsiveness, but rather are reprogrammed: after stimulation with bacterial compounds, they produce equal or even increased amounts of anti-inflammatory cytokines. Correspondingly, mRNA expression levels of genes encoding proinflammatory mediators have been reported downregulated upon stimulation with concurrent upregulation of mRNAs of anti-inflammatory mediators [2, 36]. HLA-DR expression on monocytes has been suggested as a biomarker to select sepsis patients for immune stimulatory therapy.

Epigenetic regulation of gene function likely plays a significant role in the host response to infection through suppression of proinflammatory gene expression and/or activation of anti-inflammatory genes, thereby contributing to immune suppression [41]. Protein expression can be regulated both at the pre- and posttranscriptional level. Pretranscriptional regulation takes place on chromatin, the complex formed by the DNA double helix packaged by histones. The gene loci on chromatin can be organized in transcriptionally active "euchromatin" or transcriptionally silent "heterochromatin." The chromatin activation state is regulated by histone modifications due to acetylation, methylation, ubiquitination, and phosphorylation. For example, acetylation of lysine residues within histones usually facilitates transcription [41]. "Endotoxin tolerance" in monocytes has been linked to reduced expression of marks of open chromatin such as histone H3 lysine 4 trimethylation (H3K4me3) [42], and "endotoxin tolerant" macrophages showed enhanced levels of the repressive histone modification H3K9 dimethylation (H3K9m2) at the promoter sites of the genes encoding the proinflammatory cytokines TNF and IL-1β [43]. One mechanism by which microbial stimuli induce epigenetic gene regulation is through increased expression of the histone lysine demethylase KDM6B via NF-κB activation [44]. KDM6B primes genes for transcription, and it is postulated that this promotes IL-4 maturation. The latter is a potent cytokine to counteract various proinflammatory cytokines and contributes to immune suppression. This IL-4/KDM6B axis appears to be one of the important pathways in the epigenetic regulation of macrophage activation [41]. The immune suppressive effects of sepsis can remain for months, perhaps even longer. It is hypothesized that epigenetic imprints occur both on mature immune cells in the periphery and progenitor cells in the bone marrow, thereby contributing to this long-lasting immune suppression [41].

3.5.3 Cellular Metabolism

Changes in cellular metabolism may contribute to immune suppression [45]. A shift from oxidative phosphorylation to glycolysis (the so-called Warburg effect) is important for cells to generate an inflammatory response upon stimulation by LPS, and a failure to do so may render cells relatively unresponsive. As such, a disturbed balance in cellular metabolic processes has been implicated in the altered phenotype of monocytes in sepsis, although the underlying mechanisms seem to be more intricate than

mere shifts between oxidative phosphorylation and glycolysis. In contrast to LPS (which induces a classical Warburg effect), other bacterial stimuli were found to induce a rise in both glycolysis and oxidative phosphorylation in monocytes [46]. Similarly, the deficits of monocyte metabolism in sepsis patients with immune suppression do not only involve glycolysis but include a broad inhibition of metabolic processes including glycolysis, fatty acid oxidation, and oxidative phosphorylation [47].

3.6 Microbiome

The microbiome consists of trillions of bacteria of which most are found in the gastrointestinal tract [48]. Dysbiosis of the microbiome (meaning a decreased microbial diversity) has been associated with altered immune responses (for instance, altered cytokine production capacity of immune cells). Sepsis affects the composition of the intestinal microbiome, characterized by a loss of diversity, lower abundances of key commensal genera (such as *Faecalibacterium*, *Blautia*, *Ruminococcus*), and overgrowth of opportunistic pathogens [49]. Small studies show that the gut is overrun by a single bacterial genus in patients with sepsis, most notably by *Clostridium difficile*, *Staphylococcus* spp., *Escherichia* spp., *Shigella* spp., *Salmonella* spp., and *Enterococcus* spp. [50]. This overgrowth by one genus occurs in roughly one third of the septic patients but increases with time spent on the ICU [51]. The underlying mechanism is not fully understood, but antibiotic treatment that is part of standard care in septic patients seems to have the most disruptive effect on the microbiome, possibly amplified by the use of (par)enteral feeding and gastric acid inhibitory drugs [52]. Murine studies support a role for the microbiome in regulation of granulocytosis, neutrophil homeostasis, and host resistance to sepsis [53]. In pneumonia-derived sepsis, disruption of the gut microbiome impaired host defense; underlying mechanisms likely include a reduced responsiveness to microbial stimulation and an impaired phagocytosis capacity of alveolar macrophages [54]. In addition, neutrophils from microbiota-depleted mice demonstrated a diminished capacity to migrate into inflamed tissues [55].

The immune response can further be compromised when translocation of pathological microbes through disintegrated epithelial barriers results in systemic and lymphatic spreading of pathogens. Theories of connections between the gut microbiome and distant organ function, the so-called gut-organ axis, are rapidly developing. For instance, a recent study showed evidence of gut bacteria present in the lung microbiome in mice with experimental sepsis and humans with acute respiratory distress syndrome, supporting the existence of the gut-lung axis [56]. Research concerning the pathophysiological mechanism underlying these phenomena is growing rapidly [52, 57], as are studies regarding the microbiome as a therapeutic target in critically ill patients [58].

Conclusion

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection characterized by sustained hyperinflammation

and immune suppression. While much progress has been made in understanding the pathogenesis of sepsis, translation of this knowledge into effective novel sepsis therapies has been unsuccessful. The aim of future sepsis research should be just that.

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