Hindawi Publishing Corporation
Mediators of Inflammation
Volume 2013, Article ID 165974, 16 pages
http://dx.doi.org/10.1155/2013/165974

Review Article

Cytokines in Sepsis: Potent Immunoregulators and Potential Therapeutic Targets—An Updated View

Wibke Schulte,[1,2] Jürgen Bernhagen,[2] and Richard Bucala[1]

[1] *Department of Internal Medicine, Yale University School of Medicine, The Anlyan Center, S525, P.O. Box 208031, 300 Cedar Street, New Haven, CT 06520-8031, USA*
[2] *Institute of Biochemistry and Molecular Cell Biology, University Hospital of RWTH Aachen University, Pauwelsstraße 30, 52074 Aachen, Germany*

Correspondence should be addressed to Wibke Schulte; wibke.k.schulte@gmail.com

Received 5 October 2012; Accepted 22 May 2013

Academic Editor: Celeste C. Finnerty

Sepsis and septic shock are among the leading causes of death in intensive care units worldwide. Numerous studies on their pathophysiology have revealed an imbalance in the inflammatory network leading to tissue damage, organ failure, and ultimately, death. Cytokines are important pleiotropic regulators of the immune response, which have a crucial role in the complex pathophysiology underlying sepsis. They have both pro- and anti-inflammatory functions and are capable of coordinating effective defense mechanisms against invading pathogens. On the other hand, cytokines may dysregulate the immune response and promote tissue-damaging inflammation. In this review, we address the current knowledge of the actions of pro- and anti-inflammatory cytokines in sepsis pathophysiology as well as how these cytokines and other important immunomodulating agents may be therapeutically targeted to improve the clinical outcome of sepsis.

1. Introduction

Sepsis, or the invasion of microbial pathogens into the bloodstream, is characterized by a systemic proinflammatory response, which can lead to severe sepsis and septic shock [1]. Sepsis, severe sepsis, and septic shock are major healthcare problems worldwide; they affect millions of people each year, and their incidence increases annually [2, 3]. Despite significant advances in intensive care treatment over the last years, septic shock remains associated with high mortality rates [4]. An epidemiologic study reported that septic shock is the most common cause of death in noncoronary intensive care units, and the tenth leading cause of death overall in high-income countries [2]. The outcome of sepsis is particularly unfavorable in elderly, immunocompromised, and critically ill patients [5]. Reasons for the anticipated increase in sepsis incidence and its associated mortality include the increasing number of immunocompromised patients, emerging antibiotic resistance in microorganisms, and the aging population [6].

Besides its clinical challenge, the treatment of sepsis imposes a large economic burden on healthcare systems worldwide [7]. With an estimated 750,000 cases occurring in the United States alone each year, the annual total costs have been estimated to be approximately $16.7 billion nationally [8]. Sepsis was identified as one of the five conditions that account for the most expensive hospital stays in the United States [7].

2. Definition of Sepsis

The word "sepsis" is derived from the word "*σηψις*," which in the original Greek means "decomposition" or "putrefaction," and was first mentioned in Homer's poems approximately 2700 years ago [9]. Only relatively recently have studies led to detailed descriptions of the clinical findings in septic patients and to an understanding of the underlying pathophysiology. These findings in turn have led to redefinitions of sepsis and its sequelae. Generally, sepsis is viewed as the response of the host toward invading pathogens or its toxins and is

Table 1: Diagnostic criteria for the systemic inflammatory response syndrome (SIRS).

Defined by the presence of two or more of the following clinical findings
(1) Body temperature >38°C or <36°C
(2) Heart rate >90 min^{-1}
(3) Respiratory rate >20 min^{-1} or $PaCO_2$ <32 mmHg
(4) White blood cell count >12,000 cells μL^{-1} or <4,000 cells μL^{-1} or >10% immature (band) forms

Table adapted from [11].

a syndrome that consists of multiple clinical and biochemical findings [10]. In 1991, a consensus conference was held by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) to develop a single and universally accepted definition of sepsis to improve the early diagnosis and treatment of the disease and facilitate research. A key result of this consensus conference was the introduction of the term "systemic inflammatory response syndrome" (SIRS) which was defined as a combination of clinical signs without the existence of an underlying infection [1, 11] (Table 1). SIRS can be triggered by a variety of non-infectious conditions, such as trauma, burns, hemorrhagic or hypovolemic shock, pancreatitis, and other disease states. In contrast, the diagnosis of sepsis requires clinical evidence of infection along with an underlying SIRS disease state. Severe sepsis is characterized as sepsis complicated by acute organ dysfunction, hypoperfusion, or hypotension [1]. It may lead to "multiple organ dysfunction syndrome" (MODS), or septic shock. Septic shock refers to a state of acute circulatory failure that is characterized by persistent arterial hypotension (systolic pressure <90 mmHg or a mean arterial pressure <60 mmHg) despite adequate fluid resuscitation and in the absence of other causes of hypotension [1].

Following the 1991 consensus conference, the SIRS criteria were rapidly adopted by many clinicians and scientists and were widely used to select patients for clinical trials. However, many authors criticized the SIRS diagnostic criteria for their poor specificity and lack of prognostic value, as these criteria are broad and limited in number [12–14]. In 2001, an International Sepsis Definition Conference convened aiming to evaluate the previous definitions of SIRS, sepsis, severe sepsis, and septic shock [11]. Following this conference, an expanded list of clinical and biochemical diagnostic criteria for sepsis was released, which better reflected this complex disease state. In 2004, a committee of international sepsis experts published clinical practice guidelines for the management of severe sepsis and septic shock [15]. These guidelines were widely disseminated as part of the "Surviving Sepsis Campaign" and are regularly updated, with the last revision made in 2013 [10].

3. Pathophysiology of Sepsis

In recent years, a significant body of literature has been published in an attempt to understand the complex and dynamic pathophysiologic mechanisms that underlie the heterogeneous sepsis syndrome. Sepsis has been shown to develop when the initial, appropriate host response to an infection becomes amplified and subsequently dysregulated [16], leading to an imbalance between proinflammatory and anti-inflammatory responses. It has been reported that the innate immune response, which unlike the adaptive immune response, is able to immediately respond to invading pathogens, plays a major role in the initiation of sepsis pathophysiology [17]. The activation of this "first line of cellular defense" results in an excessive release of cytokines, chemokines, and other inflammatory regulators. Cytokines regulate a variety of inflammatory responses, including the migration of immune cells to the locus of infection, which is a crucial step in containing a localized infection and preventing it from becoming systemic. However, a dysregulated cytokine release may lead to endothelial dysfunction, characterized by vasodilation and increased capillary permeability. The resulting leakage syndrome is clinically associated with hypotension, hemoconcentration, macromolecular extravasation, and edema, which are frequent findings in septic patients [18]. The dysfunctional epithelial barriers enable pathogens and their products to further invade the host organism, to disturb regulatory mechanisms, and ultimately, to cause remote organ dysfunctions [19]. Moreover, increasing evidence has indicated that immune and inflammatory responses are tightly interwoven with different physiologic processes within the human host, such as coagulation [20], metabolism [21, 22], and neuroendocrine activation [23, 24]. An inflammation-induced dysregulation of the coagulation system, for instance, significantly aggravates the deleterious effects of sepsis and can result in lethal disseminated intravascular coagulation [25].

Traditionally, sepsis was viewed as an excessive systemic proinflammatory reaction to invasive microbial pathogens. More recently, it has been proposed that the early phase of hyperinflammation is followed or overlapped by a prolonged state of immunosuppression [26–28], referred to as sepsis-induced immunoparalysis [29]. This immunoparalytic state is characterized by impaired innate and adaptive immune responses and, may play a central role in the pathogenesis of tissue damage, multiple organ failure, and death induced by sepsis.

4. Initiation of the Immune Response

The innate immune system detects invading microorganisms via pathogen recognition receptors (PRRs), which are expressed on epithelial barriers as well as on immune cells such as dendritic cells and macrophages [30] (Figure 1). A specific family of PRRs named Toll-like receptors (TLRs) recognizes conserved macromolecular motives from microorganisms, called pathogen-associated molecular patterns (PAMPs). Examples of bacterial PAMPs include lipopolysaccharide (LPS; the main virulence factor of Gram-negative bacteria), peptidoglycan, lipoteichoic acid (a cell wall component of Gram-positive bacteria), flagellin, and bacterial DNA [6, 31]. The stimulation of TLRs or the NOD-like receptor

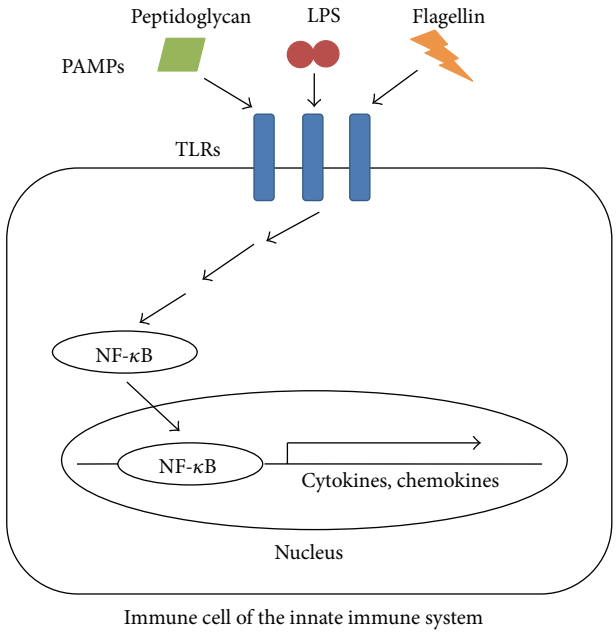

Figure 1: Initiation of the immune response following infection. Immune cells of the innate immune system recognize invading pathogens via Toll-like receptors (TLRs). The binding of pathogen-associated molecular patterns (PAMPs), such as peptidoglycan, lipopolysaccharide (LPS), or flagellin, to TLRs initiates signal transduction cascades that lead to the activation of nuclear factor κB (NF-κB). NF-κB is subsequently translocated into the nucleus where it induces the expression of cytokines and chemokines.

(NLR) family of intracellular PRRs results in the triggering of downstream signaling cascades. Depending on the particular receptor engaged, this process leads to the activation of a transcriptional response program that includes nuclear factor κB (NF-κB), followed by the production and secretion of cytokines, chemokines, and nitric oxide (NO) [32–34].

5. Cytokines in Sepsis Pathophysiology

The term cytokine describes a functional class of small protein mediators with low molecular weights (mostly <40 kDa), which are produced in a regulated fashion to affect the activation and differentiation of the immune response. Once released, proinflammatory cytokines lead to an ensuing activation of the innate or the adaptive immune response, characterized by the further production of immunoregulatory or effector cytokines [97]. The sequential release of specific cytokines is referred to as a "cytokine cascade" [98]. In the 1990s, sepsis was believed to be associated with an exacerbated release of mainly proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-12, interferon (IFN)-γ, and macrophage migration inhibitory factor (MIF). The term "cytokine storm" thus arose [99]. However, recent research on the pathophysiologic mechanisms underlying sepsis indicates that the profound proinflammatory response is counteracted by certain anti-inflammatory cytokines, including IL-10, transforming growth factor (TGF)-β, and IL-4, which attempt to restore immunological equilibrium [16, 100]. Lately, efforts have been made to identify unifying mechanisms by employing genome-wide expression data in early and late sepsis. Tang et al. reported that sepsis leads to the immediate upregulation of PRRs and the activation of signal transduction cascades [101]. However, important inflammatory markers, such as TNF-α, IL-1, or IL-10, did not show any consistent pattern in their gene expression and are highly variable in individuals. These findings suggest that the host response to sepsis is not a simple model with an initial proinflammatory phase followed by an anti-inflammatory response, but rather a highly interactive and dynamic process that may reflect heterogeneous genome-specific pathways. A tightly regulated balance in the cytokine network, which comprises proinflammatory cytokines, anti-inflammatory cytokines, and soluble inhibitors of proinflammatory cytokines, such as soluble TNF receptors (sTNFRs), IL-1 receptor antagonist (IL-1Ra), and IL-1 receptor type II (IL-1R2), is crucial for eliminating invading pathogens on the one hand and restricting excessive, tissue-damaging inflammation on the other [102, 103].

This review summarizes current knowledge of the role of cytokines in the regulation of the immune response in sepsis. The actions of individual pro- and anti-inflammatory cytokines are described in more detail and are directly associated with sepsis pathophysiology (see Table 2 for a summary). Along with the increasing knowledge of cytokine actions in recent years, a number of therapeutic strategies targeting cytokines and other immunomodulating agents have been proposed for clinical use in septic patients. Their current role in the treatment of sepsis is discussed later in this review.

6. Proinflammatory Cytokines

6.1. TNF-α and IL-1. TNF-α and IL-1 (a term used for a family of proteins, including IL-1α and IL-1β [104]) are among the most extensively studied cytokines in sepsis pathophysiology. Both are powerful proinflammatory cytokines that have been implicated in a large number of infectious and noninfectious inflammatory diseases, the latter including atherosclerosis [35], rheumatoid arthritis [36], osteoarthritis [105], and Alzheimer's disease [38]. TNF-α is a 17 kDa protein that is not only derived predominantly from activated immune cells (macrophages) but also from nonimmune cells (fibroblasts) in response to invasive, infectious, or inflammatory stimuli [37, 40]. The release of TNF-α from macrophages begins within 30 minutes after the inciting event, following gene transcription and RNA translation, which established this mediator to be an early regulator of the immune response. TNF-α acts via specific transmembrane receptors, TNF receptor (TNFR)1, and TNFR2 [106], leading to the activation of immune cells and the release of an array of downstream immunoregulatory mediators. Likewise, IL-1 is released primarily from activated macrophages in a timely manner similar to TNF-α, signals through two distinct receptors, termed IL-1 receptor type I (IL-1R1) and IL-1R2, and has comparable downstream effects on immune cells [44, 47]. The injection of

Table 2: Summary of the main features of pro- and anti-inflammatory cytokines.

Cytokine	Main sources	Main functions	Interactions with other cytokines	Alteration/involvement in diseases	Physiologic inhibitors and therapeutic targeting strategies	References
Proinflammatory						
TNF-α	Immune cells of the innate and adaptive immune system (mainly macrophages and lymphocytes); fibroblasts	Differentiation and activation of immune cells; induction of fever and coagulation; cachexia; apoptosis	Promote the release of downstream proinflammatory effector molecules	Role in atherosclerosis, RA, Alzheimer's disease, autoimmune diseases, and cancer	sTNFRs; anti-TNF Ab; TNFR inhibitors	[35–43]
IL-1	"	Induction of fever and coagulation; hematopoiesis; promotes the extravasation of inflammatory cells	"	Role in autoinflammatory diseases, heart failure, and diabetes	IL-1R2; IL-1Ra; anti-IL-1β mAb	[16, 38, 39, 44–48]
IL-6	"	Activation of B and T lymphocytes; modulation of hematopoiesis and acute phase response; induction of fever	Released in response to TNF-α and IL-1 but inhibits their release; promotes anti-inflammatory responses (sTNFRs, IL-1Ra, and TGF-β)	$\uparrow$ Serum levels following burns, major surgery, in sepsis, RA, and Crohn's disease	sIL-6R, anti-IL-6 Ab, and anti-IL-6R Ab	[49–63]
IL-12	Monocytes/macrophages; Neutrophils; dendritic cells	Promotes type 1 adaptive immune response and differentiation of T_H1 T lymphocytes; induces antitumor immune response	Induces IFN-γ production	Role in cancer	Anti-IL-12 mAb	[64–67]
IFN-γ	NK cells; T_H1 and $CD8^+$ cytotoxic T-cells	Antiviral activity; potentially reverses immunoparalysis in sepsis	Released in response to TNF-α, IL-12, and IL-18	$\uparrow$ Serum levels in sepsis	rIFN-γ	[68–73]
MIF	Pituitary cells; monocytes/macrophages	Activation of macrophages and T-cells; overrides the anti-inflammatory effect of glucocorticoids	Released in response to infection, inflammation, and proinflammatory cytokines; promotes the release of proinflammatory effector molecules	$\uparrow$ Serum levels in acute and chronic inflammatory diseases; role in cancer	Small molecule inhibitors (ISO-1, benzoxazol-2-ones); human anti-MIF Ab; MIF-derived peptide sequences	[69, 74–84]
Anti-inflammatory						
IL-10	Immune cells of the innate and adaptive immune system	Immunosuppressive properties, such as the impairment of antigen presentation and phagocytosis	Suppress the release of proinflammatory cytokines; stimulate production of sTNFRs and IL-1Ra	Dysregulated in autoimmune diseases	rIL-10	[85–88]
TGF-β	Macrophages; smooth muscle cells	Involved in tissue repair, fibrosis, and sepsis-induced immunosuppression	"	$\uparrow$ Serum levels in sepsis; upregulated in cancer and fibrosis	Small molecule inhibitors; anti-TGF-β mAb	[89–94]
IL-4	T_H2 T lymphocytes; mast cells; basophils; eosinophils	Promotes differentiation of T_H2 T lymphocytes	Induces release of IL-4 and IL-13 from macrophages	Role in scleroderma, asthma, and tuberculosis	Anti-IL-4Rα mAb	[95, 96]

RA: rheumatoid arthritis; sTNFRs: soluble TNF receptors; mAb: monoclonal antibody; IL-1Ra: IL-1 receptor antagonist; rIFN-γ: recombinant IFN-γ; ISO-1: (S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester.

TNF-α into experimental animals causes a syndrome that is largely indistinguishable from septic shock [107] and infusion of recombinant TNF-α into humans results in SIRS [108–110]. Similar results were reported for IL-1 [111–113]. TNF-α and IL-1 act synergistically to induce a shock-like state characterized by vascular permeability, severe pulmonary edema, and hemorrhage [113]. Importantly, TNF-α and IL-1 were also identified as pivotal mediators for the development of fever and, thus, belong to a group of pyrogenic cytokines [39].

A role for TNF-α and IL-1 in sepsis was demonstrated in numerous reports, including both experimental animal models of septic shock and studies in humans with sepsis. The administration of bacterial endotoxin results in the production and release of TNF-α and IL-1 into the systemic circulation, where peak concentrations are detected 60–90 min after LPS administration [114–117]. Once released, TNF-α and IL-1 act on different target cells, such as macrophages, endothelial cells, and neutrophils. TNF-α leads to an enhanced production of macrophages from progenitor cells [118], promotes the activation and differentiation of macrophages [43], and prolongs their survival [119]. All these effects enhance proinflammatory responses in sepsis. In endothelial cells, TNF-α enhances the expression of adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, and chemokines [120, 121]. TNF-α also increases integrin adhesiveness in neutrophils and promotes their extravasation into tissues. TNF-α and IL-1 were identified as the main mediators of inflammation-induced activation of coagulation, with TNF-α having a potent upregulating action on endothelial expression of procoagulant [42]. In addition, TNF-α and IL-1 amplify inflammatory cascades in an autocrine and paracrine manner by activating macrophages to secrete other proinflammatory cytokines (IL-6, IL-8, and MIF), lipid mediators, and reactive oxygen and nitrogen species [16, 46], leading to sepsis-induced organ dysfunction. Because of its unique ability to orchestrate downstream cytokine cascade, TNF-α is considered to be a "master regulator" of inflammatory cytokine production [37], while the important regulatory role of IL-1 in inflammation is widely accepted as well.

Soluble cytokine receptors and receptor antagonists, termed sTNFRs, IL-1R2, and IL-1Ra, were identified for TNF-α and IL-1, which modulate the actions of these cytokines. Elevated levels of sTNFRs and IL-1Ra were measured in the systemic circulation of healthy volunteers administered endotoxin [122, 123], and in septic patients, in whom sTNFRs and IL-1Ra plasma concentrations also correlated with disease severity, and in the case of sTNFRs, with mortality [124–126]. In different murine models of septic shock, the administration of IL-1Ra increased survival, suggesting a therapeutic effect for IL-1Ra [48, 127]. For sTNFRs, it was proposed that the ratio between TNF-α and sTNFRs, rather than the absolute plasma concentration of TNF-α or sTNFRs alone, has prognostic value in septic patients [41]. This indicates that a tight balance between cytokines and their soluble inhibitors is crucial for a positive outcome of sepsis. However, the exact mechanisms underlying this balance remain incompletely understood.

6.2. IL-6. IL-6 is a 21 kDa glycoprotein produced by a wide variety of cells, especially macrophages, dendritic cells, lymphocytes, endothelial cells, fibroblasts, and smooth muscle cells in response to stimulation with LPS, IL-1, and TNF-α [53–56]. Elevated IL-6 concentrations are measured in many acute conditions, such as burns, major surgery and sepsis [52], and peak subsequent to TNF-α and IL-1 concentrations [123, 128]. Plasma levels of IL-6 are stably elevated in these conditions and correlate with many indicators of disease severity such as clinical scores [129], stress after surgery [130] and trauma [131], the occurrence of multiple organ failure and septic shock [132, 133], and the overall mortality [134].

IL-6 has a variety of biological effects, including the activation of B and T lymphocytes and the coagulation system, and the modulation of hematopoiesis [49, 61]. In contrast to TNF-α and IL-1, the injection of IL-6 by itself does not produce a sepsis-like state [135]. A key function of IL-6 is the induction of fever [50] and the mediation of the acute phase response [51, 59], a systemic reaction to an inflammatory stimulus that is characterized by fever, leukocytosis, and the release of hepatic acute phase proteins such as C-reactive protein, complement components, fibrinogen, and ferritin [136]. *In vivo* studies in *Il-6*-knockout mice demonstrated that the deletion of the *Il-6* gene decreases lung inflammation in a model of acute lung injury [137] and protects from mortality and the development of organ failure in a zymosan-induced acute peritoneal inflammation [138]. More recently, Pathan et al. showed that IL-6 causes myocardial depression in meningococcal disease [139]. Myocardial dysfunction in septic shock leads to impaired tissue perfusion, multiorgan failure, and death.

Despite its proinflammatory properties, IL-6 also has been shown to promote anti-inflammatory responses. IL-6 inhibits the release of TNF-α and IL-1 [57] and enhances the circulation levels of anti-inflammatory mediators, such as IL-1Ra, sTNFRs, IL-10, TGF-β, and cortisol [58, 60, 62]. A protective effect of IL-6 was shown in experimental endotoxemia [140, 141], whereas the genetic deletion of IL-6 did not alter the mortality in a model of polymicrobial sepsis induced by cecal ligation and puncture (CLP) [142].

6.3. IL-12. Phagocytes (monocytes/macrophages and neutrophils) and dendritic cells are the major sources of the heterodimeric cytokine IL-12 [66, 67], which is structurally related to the IL-6 cytokine family [143]. IL-12 regulates innate immune responses and promotes the development of a type 1 adaptive immune response, which is characterized by enhanced mononuclear phagocyte responses. Thus, IL-12 links early, nonspecific, and later, specific immune responses. Upon release, IL-12 induces T-cells and natural killer (NK) cells to produce IFN-γ, which directly activates macrophages to enhance their bactericidal activity and produce additional T helper 1 (T_H1) cytokines [64]. Additionally, IL-12 stimulates the differentiation of naive $CD4^+$ T-cells into T_H1 cells and protects them from antigen-induced apoptotic death [65]. IL-12 also increases the proliferation and colony formation of hematopoietic progenitors.

Despite many years of research, the role of IL-12 in sepsis remains controversial. Initially, animal models of sepsis were employed to investigate its role in sepsis. Increased plasma IL-12 concentrations were measured in animals following the administration of LPS or *Escherichia coli*, and after polymicrobial sepsis induced by CLP [144–146]. The immunoneutralization or genetic deletion of IL-12 resulted in an increased mortality of mice undergoing CLP, with a subsequent decrease in IFN-γ and an increase in IL-10 levels [144, 147]. However, in a different animal model, an increase in LPS-induced mortality was observed in mice transiently overexpressing IL-12 and the neutralization of IL-12 improved survival following LPS challenge [145]. Clinically, a prospective study in patients undergoing major visceral surgery suggested that a selective defect in preoperative monocyte IL-12 production impairs the host defense against postoperative infections and, thus, increases the risk of lethal sepsis [148]. Likewise, it was reported that survivors from severe sepsis produce more IL-12 from LPS-stimulated peripheral blood mononuclear cells (PBMCs) than nonsurvivors [149], and that they show serial increases in their IL-12 response from PBMCs [150].

6.4. IFN-γ. IFN-γ is mainly produced by activated NK cells, T_H1, and $CD8^+$ cytotoxic T cells [68]. Its production is tightly regulated and stimulated by macrophage-derived cytokines, especially TNF-α, IL-12, and IL-18 [72]. IFN-γ was discovered due to its antiviral activity [73]. Subsequently, the important immunoregulatory role of IFN-γ to a wider range of pathogens became evident. Mice lacking IFN-γ were shown to be more susceptible to intracellular pathogens, such as *Leishmania major* [151], *Listeria monocytogenes* [152], Mycobacteria [153], and different viruses [154]. The neutralization of IFN-γ or its receptor makes mice more resistant to an LPS-induced shock [155, 156]. IFN-γ is normally not detectable in the plasma of healthy humans, but its levels can be elevated in patients with sepsis [69]. Plasma levels of IFN-γ do not correlate with sepsis severity or mortality. Recently, a role for IFN-γ in the reversal of sepsis-induced immunoparalysis was reported. During the immunoparalytic state, macrophages were shown to display impaired phagocyte functions and to release reduced amounts of T_H1-promoting cytokines upon stimulation with bacterial products [157, 158]. Flohé et al. showed that IFN-γ, as well as granulocyte-macrophage colony-stimulating factor (GM-CSF), was able to restore macrophage function in macrophages taken from septic mice upon bacterial stimulation *ex vivo* [70]. Likewise, a recently published *in vivo* study in humans demonstrated that IFN-γ partially reverses immunoparalysis, identifying IFN-γ as a potential new treatment option for sepsis [71].

6.5. MIF. MIF is a pleiotropic proinflammatory cytokine, which is responsible for the first cytokine activity to be discovered [159]. MIF is released by pituitary cells in response to LPS and stress [74, 77] and by immune cells (most importantly monocytes and macrophages) after exposure to various infectious and inflammatory stimuli, including LPS, TNF-α, and IFN-γ [78, 160]. Uniquely among innate cytokines, MIF is present in preformed pools within cells and is rapidly released upon proinflammatory and stress stimulation [161]. This release response of the preformed protein is followed by MIF gene transcription and RNA translation, which replenishes intracellular stores. The Golgi complex-associated protein p115 was identified as an intracellular binding partner for MIF that is essential for its secretion [161]. Once secreted, MIF increases macrophage antimicrobial responses by increasing macrophage survival [83], elevating TLR4 expression on macrophages [162] and promoting macrophage inflammatory recruitment [75]. MIF also promotes the secretion of downstream cytokines, such as TNF-α, IFN-γ, and IL-1, and it promotes the activation of T cells [80]. MIF activates immune cells by binding to CD74 (the cell surface form of the class II-associated invariant chain), which leads to the recruitment of CD44 into a signaling complex and the downstream initiation of the ERK1/2 MAP kinase pathway [163, 164]. Additionally, MIF engages the chemokine receptors CXCR2 and CXCR4 in a high affinity, noncognate interaction [75]. While the precise signaling mechanisms of MIF through these receptors are yet to be clarified, it was demonstrated that the MIF/CXCR axis is critical for MIF-dependent monocyte recruitment processes in atherosclerotic arteries [75]. MIF's critical role within the immune system is further underscored by the finding that MIF is induced by low concentrations of glucocorticoids and has the unique ability to override the anti-inflammatory and immunosuppressive effects of glucocorticoids [77, 81, 84]. Mouse modeling and human clinical studies have implicated MIF in the pathogenesis of various acute and chronic inflammatory diseases, including septic shock [79], asthma [165], rheumatoid arthritis [166], atherosclerosis [167], inflammatory bowel disease [168], and cancer [76].

The actions of MIF in sepsis pathophysiology have been studied extensively. The administration of recombinant MIF protein increases mortality following LPS administration [74]. Conversely, several studies showed that the neutralization of MIF reduced proinflammatory cytokine production, decreased organ injury, and increased the survival rate of mice in different animal models of sepsis, such as endotoxic shock, *Escherichia coli* injection or CLP [79, 169–172]. Recently, MIF was established as an important mediator of LPS-induced myocardial dysfunction [173, 174]. Serum MIF concentration of patients suffering from sepsis are significantly higher compared to healthy individuals [175] and correlate with the outcome [176]. Thus, MIF was suggested as an early predictor for survival in septic patients [177]. In the largest genetic study of sepsis performed to date, *MIF* alone among 20 candidate polymorphic loci within immune response genes was associated with clinical outcome from septic shock [178]. Notably, the role for *MIF* gene variants in this study of community-acquired pneumonia progressing to sepsis was found to be one of protection, with a 50% survival benefit observed in individuals with high expression *MIF* alleles at 30, 60, and 90 days of followup. Thus, despite prior suggestions that sepsis pathology results from an excessive or overreactive systemic inflammatory response, high MIF expression was protective, presumably

because of its high upstream role in eliminating invasive microbial infections or because of its ability to counteract the immunoparalytic state. A strong role for MIF also has been reported for clinical outcome from meningococcemia [179], invasive streptococcal infection [180], and severe malaria [181].

Very recently, the protein D-dopachrome tautomerase (D-DT), which is the only known MIF homolog in the human genome, was identified as a cytokine [82, 175]. While the precise biologic functions of D-DT (a.k.a. MIF-2) are yet to be clarified, it was demonstrated that D-DT is released in response to LPS and that its immunoneutralization protects mice from lethal endotoxic shock. This protective action of anti-D-DT was associated with a reduction in the circulating levels of TNF-α, IFN-γ, IL-12, and IL-1 and increases in the serum concentration of IL-10. D-DT serum levels have been determined to be higher in septic patients compared to healthy controls and to correlate with MIF and with disease severity.

7. Anti-Inflammatory Cytokines

7.1. IL-10. IL-10 is a 35-kDa homodimeric cytokine that is produced by many types of immune cells, such as monocytes, macrophages, B and T lymphocytes, and NK cells [87]. Functional studies widely revealed anti-inflammatory functions of IL-10. *In vitro*, IL-10 suppresses the production of proinflammatory mediators, such as TNF-α, IL-1, IL-6, IFN-γ, and GM-CSF, in immune cells [85, 86]. In contrast, it was reported that IL-10 has no effect on the constitutive expression of TGF-β, a cytokine with anti-inflammatory properties. Additionally, IL-10 stimulates the production of IL-1Ra and sTNFRs, thereby neutralizing the proinflammatory actions of IL-1 and TNF [88]. These results were supported *in vivo*. In an experimental murine model, the administration of recombinant IL-10 protein protected mice from lethal endotoxemia, even when IL-10 was injected 30 minutes after the LPS administration [182]. In contrast, the immunoneutralization of IL-10 led to elevated levels of circulating TNF-α and IL-6 in mice [183] and reversed the ability of IL-10 to protect mice from lethal endotoxemia [182]. Despite these clearly protective effects of IL-10 in LPS-induced pathologies, the actions of IL-10 were not always beneficial in the CLP model of polymicrobial sepsis. In fact, the inhibition of IL-10 12 hours after CLP markedly improved survival [184]. However, the administration of neutralizing IL-10 antibodies at the time of CLP partially exacerbated mortality [185]. These findings indicate that the time of anti-IL-10 antibody application is crucial for the outcome, and that IL-10 can exhibit protective or harmful effects in the course of sepsis. More recently, Latifi et al. reported that IL-10-deficient mice showed an earlier onset of lethality following CLP and showed a reduced response to rescue surgery (the removal of the necrotic cecum) compared with wildtype mice [87]. However, the administration of recombinant IL-10 protein to WT or IL-10 deficient mice increased survival and lengthened the therapeutic window for the rescue surgery. These results suggest that IL-10 might regulate the transition from early reversible sepsis to late irreversible septic shock. Recently, it was investigated whether polymorphisms in the IL-10 gene promotor affect sepsis susceptibility. Zeng et al. showed that the –1082A allele was associated with a lower IL-10 production following LPS stimulation and with the development of sepsis after major trauma [186].

7.2. TGF-β. TGF-β is a member of a family of dimeric polypeptide growth factors and is an important anti-inflammatory cytokine. A role for TGF-β was demonstrated in tissue repair und fibrosis [93], as well as in sepsis-induced immunosuppression [89]. *In vitro*, TGF-β suppresses the release of proinflammatory mediators, such as IL-1, TNF-α, and HMGB1, from monocytes and macrophages [90, 92], and stimulates the production of immunosuppressive factors such as sTNFRs and IL-1Ra [94]. TGF-β also inhibits T lymphocyte functions, such as IL-2 secretion and T cell proliferation [187], and it promotes the development of T regulatory cells [188]. Moreover, studies demonstrated a role of TGF-β, as well as IL-10, in the tolerance of monocytes and macrophages to LPS, which is characterized by a downregulated cytokine response following a second LPS challenge [189].

In alignment with the *in vitro* studies, experiments in animal models of sepsis and clinical studies in humans supported the anti-inflammatory actions of TGF-β. Parrella et al. reported that treatment with TGF-β blocked endotoxin-induced hypotension, potentially by inhibiting the hypotensive effects of NO and improved survival in a rat model of *Salmonella typhosa* endotoxin-induced septic shock [190]. Similar results were reported in a rat model using the endotoxin of *Salmonella enteritidis* [191] and in the murine endotoxic shock model [192]. Moreover, patients with sepsis had elevated levels of TGF-β compared to healthy controls [91]. TGF-β levels were shown to peak early in disease progression and not to correlate strongly with disease severity or prognosis [193]. Recent data demonstrated that TGF-β reverses the depression of cardiac myocyte contraction, which is induced by proinflammatory cytokines, such as TNF-α and IL-1, and by serum from patients with septic shock [194]. This suggests that TGF-β might have cardioprotective effects in sepsis-induced cardiac injury.

7.3. IL-4. IL-4 is a cytokine with many immunoregulatory functions, which was shown to participate in the regulation of proliferation, differentiation, and apoptosis of multiple cell types [195–197]. An important action of IL-4 is its critical role in the regulation of T lymphocyte differentiation, in which it promotes T_H2 cell differentiation while inhibiting T_H1 cell differentiation [96]. IL-4 is the principal cytokine produced by T_H2 lymphocytes, causes an enhanced release of further IL-4 and other anti-inflammatory cytokines, and suppresses the secretion of monocyte-derived proinflammatory cytokines [95].

Animal-based studies revealed that IL-4 increases survival of mice exposed to lethal doses of LPS [198]. However, protective as well as detrimental effects of IL-4 were described in *Staphylococcus aureus*-triggered murine sepsis, which appeared to depend on the host's genetic background [199].

In humans, it was reported that the mRNA expression of IL-4 was associated with survival of patients with severe sepsis, but that the plasma IL-4 levels in septic patients on the day of admission to the hospital did not differ between survivors and nonsurvivors [200]. Recently, it was suggested that *IL-4* promoter polymorphisms might affect the balance between the T_H1 and T_H2 immune response, and thereby predispose trauma patients to the development of sepsis [201]. While all these studies indicate that IL-4 plays an important role in the pathogenesis of sepsis, its precise role during the course of disease remains unknown.

8. Immunomodulating Treatment Strategies for Sepsis

Basic research and clinical studies performed over the past several years have led to a significant amount of data on immunoregulatory and modulating mechanisms in sepsis. Cytokines have proved to function as important regulators of the immune response, while various other agents, including growth factors or activated protein C (APC), have shown immunomodulating effects. Therefore, it would appear to be highly promising and beneficial to therapeutically target these mediators in order to decrease the unfavorable effects of sepsis-related host responses, and to improve the overall outcome. A number of potential therapeutic targets have been identified to date, and their clinical use has subsequently been assessed in sepsis, both in animal models and in clinical trials. The following paragraphs will give an overview of recent important therapeutic strategies for the treatment of sepsis with special respect to anticytokine approaches.

8.1. Anti-TNF-α and Anti-IL-1. In one of the first approaches of treating sepsis, therapies were directed against TNF-α and IL-1. These therapies included monoclonal antibodies against TNF-α [202], sTNFRs [45], IL-1Ra, and soluble IL-1 receptors [203]. While positive results were obtained in experimental models of sepsis, these agents failed to decrease the overall mortality of septic patients in clinical trials [204, 205]. Theses clinical results were unexpected, as the powerful cytokines TNF-α and IL-1 had been shown to initiate the excessive inflammatory immune response in sepsis, which was believed to cause the deleterious effects on the host organism. Subsequent studies were conducted to explain the lack of success of TNF-α and IL-1 blocking agents in clinical trials. Among many potential reasons, it was reported that the circulating levels of "early" cytokines like TNF-α and IL-1 return to almost baseline levels within the first few hours during the progression of disease [206]. Thus, the specific inhibition of "early" cytokines may provide only a narrow window for clinical intervention. Moreover, the elevation of their circulating levels may be downregulated even before the diagnosis of sepsis is made [207], indicating that the early diagnosis of sepsis is crucial for the outcome. It was proposed that inhibiting cytokines like MIF, whose immunoneutralization protected mice from lethal peritonitis even when the antibodies were administered after the onset of disease [79], or HMGB1, which may be involved in later stages of sepsis, might be beneficial in reducing sepsis mortality.

8.2. Anti-MIF. Given the complex role of MIF in various pathologies, such as sepsis, MIF is under investigation as a target for the development of novel pharmacological agents. Crystallographic studies of human MIF have identified a tautomerase enzymatic activity site that is important for MIF's cytokine activities [169, 208]. This offers the unique possibility to target a cytokine by a small molecule approach. In fact, small molecules like ISO-1 [(S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester] were found to inhibit this catalytic site and to block MIF interaction with its receptor [209] and its downstream effects. ISO-1 suppresses the MIF-induced activation of NF-κB (although NF-κB has so far not emerged as the predominant pathway induced by MIF) and the MIF-induced production of TNF-α from macrophages *in vitro* [169]. *In vivo*, the administration of ISO-1 dose-dependently improves survival in a murine model of lethal endotoxemia and rescues mice from polymicrobial sepsis, even when the ISO-1 treatment is started 24 hours after the CLP surgery [169]. ISO-1 or anti-MIF monoclonal antibody administration also was beneficial in a model of lethal flavivirus infection [210]. The positive results obtained from animal models have helped to prompt the clinical development of specific MIF blocking agents. Currently, a human anti-MIF antibody is in clinical development [211], and small molecule MIF inhibitors such as potent benzoxazol-2-ones are advancing towards clinical application [209, 212]. MIF-derived peptide sequences targeting MIF/receptor interfaces also have been considered as potential strategies [213].

8.3. IFN-γ- and GM-CSF-Directed Strategies. In light of recent research indicating that an immunosuppressive state may contribute to sepsis pathophysiology, it may be advantageous to apply IFN-γ or growth factors, such as GM-CSF, in order to restore the host immune functions. Clinical studies showed that GM-CSF improved the gas exchange in patients with severe sepsis associated with respiratory dysfunction [214] and resulted in a more effective anti-infectious defense [215]. However, in neither study did treatment with GM-CSF improve mortality. Also, IFN-γ given intravenously to severely injured patients was not successful in decreasing infection rates or improving survival [216].

8.4. APC-Directed Strategies. Numerous studies have revealed functional interactions between inflammation and coagulation that contribute significantly to sepsis pathophysiology [20, 217]. Inflammation mediates the coagulation cascade, leading in the extreme case to the development of disseminated intravascular coagulation, and clotting factors in return reciprocally modulate the local or the systemic inflammatory response. Therefore, therapeutic intervention in the coagulation pathway might not only counteract the deleterious effects attributed to a dysregulated coagulation system but also affect the dysregulated inflammatory and immune response in a beneficial manner.

Recombinant human activated protein C (rhAPC) was the first biological drug for the treatment of sepsis that was approved by the Food and Drug Administration in the United States. Protein C is produced by the liver as an acute phase zymogen and is subsequently activated by thrombin [218]. Upon its activation, APC proteolytically inactivates factors Va and VIIIa of the coagulation cascade, resulting in a decrease in thrombin production. Low thrombin levels ultimately lead to the inhibition of the thrombin-induced platelet activation. These anticoagulant actions of APC were considered initially to be responsible for its beneficial effect in sepsis. However, more recent studies have suggested an additional anti-inflammatory action of APC. By preventing the excessive generation of thrombin, APC reduces thrombin's strong proinflammatory actions [219], which include the release of chemokines and cytokines (such as MIF) and the expression of adhesion molecules on platelets and endothelium [220]. Moreover, APC was shown to inhibit chemotaxis and IL-6 release by human neutrophils [221] and to prevent the production of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, MIF, and IL-8 by LPS-stimulated monocytes [222, 223]. Antiapoptotic functions have also been attributed to APC. Bilbault et al. showed that circulating mononuclear cells from septic shock patients treated with rhAPC had decreased Bax/Bcl-2 protein ratios compared to healthy controls [224]. Low Bax/Bcl-2 protein ratios are found in antiapoptotic states, which might be beneficial in the recovery from sepsis as high apoptotic rates of immune cells were shown to contribute to the immunoparalytic state of sepsis [225].

Following preclinical investigations of septic shock showing that the administration of APC improved survival [226], the first reports describing the impact of rhAPC administration in humans with severe sepsis were published in 2001. Bernard et al. reported that a 96-hour continuous infusion of rhAPC, also referred to as drotrecogin alfa (activated) (DrotAA), markedly reduced the circulating levels of D-dimers (fibrin degradation products) and IL-6 in patients with severe sepsis [227]. The PROWESS phase 3 clinical trial subsequently showed that the treatment of severe sepsis with rhAPC reduced the relative and absolute death risk by 19.4 and 6.1%, respectively [228]. However, an increased incidence of serious bleeding events was observed in the rhAPC-treated group compared to the placebo group. Nonetheless, on the strength of the survival results, rhAPC was approved for clinical use. Because subgroup analysis in the PROWESS study showed that reduced mortality in the rhAPC-treated group was limited to patients with high disease severity, for instance, those with at least two sepsis-induced dysfunctional organs or those with a high acute physiology and chronic health evaluation (APACHE) II score, the international guidelines for the management of severe sepsis, and septic shock released in 2008 recommended that rhAPC only be used for patients at high risk of death [229]. Unfortunately, more recently published results from the follow-up PROWESS-SHOCK trial indicated that rhAPC did not significantly reduce mortality of patients with septic shock. In fact, at both 28 and 90 days after the initiation of treatment, there was no significant difference in the mortality rate between septic patients treated with rhAPC and those given a placebo (26.4 versus 24.2% and 34.1 versus 32.7%, resp.) [230]. These results have now led to the withdrawal of rhAPC from the market. Future studies will be required to clarify whether rhAPC ultimately finds clinical utility, perhaps in a carefully defined subset of subjects with sepsis. Current treatment modalities for sepsis remain largely supportive rather than directly immunomodulating.

9. Conclusion

Sepsis remains a major challenge both for clinicians and researchers. Despite many years of intensive research and numerous clinical studies, its pathophysiology is still incompletely understood, and specific anticytokine treatments have not been successful in clinical trials. This is mainly due to the fact that sepsis can be characterized as a complex and dynamic disease process that involves excessive and suppressed inflammatory and immune responses. Moreover, it affects heterogeneous patient populations with diverse disease etiologies and comorbidities, further aggravating our difficulties in understanding and therapeutically intervening in this complex syndrome. Nonetheless, research studies have elucidated many different pathophysiologic processes involved in sepsis and have revealed an important regulatory role of pro- and anti-inflammatory cytokines in disease progression. These findings have led to the development of promising anticytokine and immunomodulating treatment strategies. We anticipate that ongoing research will expand our knowledge of currently described disease mechanisms and lead to the identification of new pathophysiologic features of sepsis. Also, we expect that novel antisepsis strategies will continue to be clinically assessed and potentially exploited for the more effective future treatment of sepsis.

Acknowledgments

The authors were supported by the Deutsche Forschungsgemeinschaft (DFG) Grant SCHU2851/1-1 (to Wibke Schulte), DFG Grants BE1977/4-2 and SFB-TRR57/P07 (to Jürgen Bernhagen), and the National Institutes of Health Grant NIH RO1AI042310 (to Richard Bucala).

References

[1] R. C. Bone, R. A. Balk, F. B. Cerra et al., "Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine," *Chest*, vol. 101, no. 6, pp. 1644–1655, 1992.

[2] D. C. Angus, W. T. Linde-Zwirble, J. Lidicker, G. Clermont, J. Carcillo, and M. R. Pinsky, "Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care," *Critical Care Medicine*, vol. 29, no. 7, pp. 1303–1310, 2001.

[3] G. S. Martin, D. M. Mannino, S. Eaton, and M. Moss, "The epidemiology of sepsis in the United States from 1979 through 2000," *The New England Journal of Medicine*, vol. 348, no. 16, pp. 1546–1554, 2003.

[4] V. Y. Dombrovskiy, A. A. Martin, J. Sunderram, and H. L. Paz, "Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003," *Critical Care Medicine*, vol. 35, no. 5, pp. 1244–1250, 2007.

[5] R. Anel and A. Kumar, "Human endotoxemia and human sepsis: limits to the model," *Critical Care*, vol. 9, no. 2, pp. 151–152, 2005.

[6] T. van der Poll and S. M. Opal, "Host-pathogen interactions in sepsis," *The Lancet Infectious Diseases*, vol. 8, no. 1, pp. 32–43, 2008.

[7] A. N. Chalupka and D. Talmor, "The economics of sepsis," *Critical Care Clinics*, vol. 28, no. 1, pp. 57–76, 2012.

[8] H. Burchardi and H. Schneider, "Economic aspects of severe sepsis: a review of intensive care unit costs, cost of illness and cost effectiveness of therapy," *PharmacoEconomics*, vol. 22, no. 12, pp. 793–813, 2004.

[9] S. Geroulanos and E. T. Douka, "Historical perspective of the word 'sepsis'," *Intensive Care Medicine*, vol. 32, no. 12, p. 2077, 2006.

[10] R. P. Dellinger, M. M. Levy, A. Rhodes et al., "Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012," *Critical Care Medicine*, vol. 41, no. 2, pp. 580–637, 2013.

[11] M. M. Levy, M. P. Fink, J. C. Marshall et al., "2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference," *Critical Care Medicine*, vol. 31, no. 4, pp. 1250–1256, 2003.

[12] C. Alberti, C. Brun-Buisson, S. V. Goodman et al., "Influence of systemic inflammatory response syndrome and sepsis on outcome of critically III infected patients," *American Journal of Respiratory and Critical Care Medicine*, vol. 168, no. 1, pp. 77–84, 2003.

[13] C. Alberti, C. Brun-Buisson, S. Chevret et al., "Systemic inflammatory response and progression to severe sepsis in critically ill infected patients," *American Journal of Respiratory and Critical Care Medicine*, vol. 171, no. 5, pp. 461–468, 2005.

[14] D. Pittet, S. Rangel-Frausto, N. Li et al., "Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients," *Intensive Care Medicine*, vol. 21, no. 4, pp. 302–309, 1995.

[15] R. P. Dellinger, J. M. Carlet, H. Masur et al., "Surviving sepsis campaign guidelines for management of severe sepsis and septic shock," *Critical Care Medicine*, vol. 32, no. 3, pp. 858–873, 2004.

[16] J. Cohen, "The immunopathogenesis of sepsis," *Nature*, vol. 420, no. 6917, pp. 885–891, 2002.

[17] J. D. Hansen, L. N. Vojtech, and K. J. Laing, "Sensing disease and danger: a survey of vertebrate PRRs and their origins," *Developmental and Comparative Immunology*, vol. 35, no. 9, pp. 886–897, 2011.

[18] E. Rivers, B. Nguyen, S. Havstad et al., "Early goal-directed therapy in the treatment of severe sepsis and septic shock," *The New England Journal of Medicine*, vol. 345, no. 19, pp. 1368–1377, 2001.

[19] S. Denk, M. Perl, and M. Huber-Lang, "Damage- and pathogen-associated molecular patterns and alarmins: keys to sepsis?" *European Surgical Research*, vol. 48, no. 4, pp. 171–179, 2012.

[20] M. Levi and T. van der Poll, "Inflammation and coagulation," *Critical Care Medicine*, vol. 38, supplement 2, pp. S26–S34, 2010.

[21] T. Atsumi, Y. Cho, L. Leng et al., "The proinflammatory cytokine macrophage migration inhibitory factor regulates glucose metabolism during systemic inflammation," *The Journal of Immunology*, vol. 179, no. 8, pp. 5399–5406, 2007.

[22] B. Mlinar and J. Marc, "New insights into adipose tissue dysfunction in insulin resistance," *Clinical Chemistry and Laboratory Medicine*, vol. 49, no. 12, pp. 1925–1935, 2011.

[23] M. Emonts, F. C. G. J. Sweep, N. Grebenchtchikov et al., "Association between high levels of blood macrophage migration inhibitory factor, inappropriate adrenal response, and early death in patients with severe sepsis," *Clinical Infectious Diseases*, vol. 44, no. 10, pp. 1321–1328, 2007.

[24] L. Capuron and A. H. Miller, "Immune system to brain signaling: neuropsychopharmacological implications," *Pharmacology and Therapeutics*, vol. 130, no. 2, pp. 226–238, 2011.

[25] K. M. Hook and C. S. Abrams, "The loss of homeostasis in hemostasis: new approaches in treating and understanding acute disseminated intravascular coagulation in critically ill patients," *Clinical and Translational Science*, vol. 5, no. 1, pp. 85–92, 2012.

[26] R. S. Hotchkiss and D. W. Nicholson, "Apoptosis and caspases regulate death and inflammation in sepsis," *Nature Reviews Immunology*, vol. 6, no. 11, pp. 813–822, 2006.

[27] H. Volk, P. Reinke, and W. Döcke, "Clinical aspects: from systemic inflammation to 'immunoparalysis'," *Chemical Immunology*, vol. 74, pp. 162–177, 2000.

[28] R. N. Germain, "Maintaining system homeostasis: the third law of Newtonian immunology," *Nature Immunology*, vol. 13, no. 10, pp. 902–906, 2012.

[29] R. S. Hotchkiss and S. Opal, "Immunotherapy for sepsis—a new approach against an ancient foe," *The New England Journal of Medicine*, vol. 363, no. 1, pp. 87–89, 2010.

[30] S. Akira, S. Uematsu, and O. Takeuchi, "Pathogen recognition and innate immunity," *Cell*, vol. 124, no. 4, pp. 783–801, 2006.

[31] K. J. Ishii, S. Koyama, A. Nakagawa, C. Coban, and S. Akira, "Host innate immune receptors and beyond: making sense of microbial infections," *Cell Host and Microbe*, vol. 3, no. 6, pp. 352–363, 2008.

[32] S. Akira and K. Takeda, "Toll-like receptor signalling," *Nature Reviews Immunology*, vol. 4, no. 7, pp. 499–511, 2004.

[33] S. A. Lakhani and C. W. Bogue, "Toll-like receptor signaling in sepsis," *Current Opinion in Pediatrics*, vol. 15, no. 3, pp. 278–282, 2003.

[34] L. A. J. O'Neill, "A critical role for citrate metabolism in LPS signalling," *Biochemical Journal*, vol. 438, no. 3, pp. e5–e6, 2011.

[35] J. Jawien, "New insights into immunological aspects of atherosclerosis," *Polskie Archiwum Medycyny Wewnetrznej*, vol. 118, no. 3, pp. 127–131, 2008.

[36] E. Choy, "Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis," *Rheumatology*, vol. 51, supplement 5, pp. v3–v11, 2012.

[37] N. Parameswaran and S. Patial, "Tumor necrosis factor-a signaling in macrophages," *Critical Reviews in Eukaryotic Gene Expression*, vol. 20, no. 2, pp. 87–103, 2010.

[38] J. M. Rubio-Perez and J. M. Morillas-Ruiz, "A review: inflammatory process in Alzheimer's disease, role of cytokines," *The Scientific World Journal*, vol. 2012, Article ID 756357, 15 pages, 2012.

[39] C. A. Dinarello, "Infection, fever, and exogenous and endogenous pyrogens: some concepts have changed," *Journal of Endotoxin Research*, vol. 10, no. 4, pp. 201–222, 2004.

[40] M. Feldmann, F. M. Brennan, M. Elliott, P. Katsikis, and R. N. Maini, "TNFα as a therapeutic target in rheumatoid arthritis," *Circulatory Shock*, vol. 43, no. 4, pp. 179–184, 1994.

[41] B. Modzelewski, "The role of soluble TNF p55 and p75 receptors in the development of septic syndrome," *Polski Merkuriusz Lekarski*, vol. 14, no. 79, pp. 69–72, 2003.

[42] M. Schouten, W. J. Wiersinga, M. Levi, and T. van der Poll, "Inflammation, endothelium, and coagulation in sepsis," *Journal of Leukocyte Biology*, vol. 83, no. 3, pp. 536–545, 2008.

[43] A. L. Witsell and L. B. Schook, "Tumor necrosis factor alpha is an autocrine growth regulator during macrophage differentiation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 89, no. 10, pp. 4754–4758, 1992.

[44] C. A. Dinarello, "Proinflammatory and anti-inflammatory cytokines as mediators in the pathogenesis of septic shock," *Chest*, vol. 112, supplement 6, pp. 321S–329S, 1997.

[45] C. J. Fisher Jr., J. M. Agosti, S. M. Opal et al., "Treatment of septic shock with the tumor necrosis factor receptor: Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group," *The New England Journal of Medicine*, vol. 334, no. 26, pp. 1697–1702, 1996.

[46] Y. Fong, K. J. Tracey, L. L. Moldawer et al., "Antibodies to cachectin/tumor necrosis factor reduce interleukin 1β and interleukin 6 appearance during lethal bacteremia," *Journal of Experimental Medicine*, vol. 170, no. 5, pp. 1627–1633, 1989.

[47] L. A. J. O'Neill, "The interleukin-1 receptor/Toll-like receptor superfamily: 10 years of progress," *Immunological Reviews*, vol. 226, no. 1, pp. 10–18, 2008.

[48] K. Ohlsson, P. Bjork, M. Bergenfeldt, R. Hageman, and R. C. Thompson, "Interleukin-1 receptor antagonist reduces mortality from endotoxin shock," *Nature*, vol. 348, no. 6301, pp. 550–552, 1990.

[49] E. C. Borden and P. Chin, "Interleukin-6: a cytokine with potential diagnostic and therapeutic roles," *Journal of Laboratory and Clinical Medicine*, vol. 123, no. 6, pp. 824–829, 1994.

[50] Z. Chai, S. Gatti, C. Toniatti, V. Poli, and T. Bartfai, "Interleukin (IL)-6 gene expression in the central nervous system is necessary for fever response to lipopolysaccharide or IL-1β: a study on IL- 6-deficient mice," *Journal of Experimental Medicine*, vol. 183, no. 1, pp. 311–316, 1996.

[51] M. Kopf, H. Baumann, G. Freer et al., "Impaired immune and acute-phase responses in interleukin-6-deficient mice," *Nature*, vol. 368, no. 6469, pp. 339–342, 1994.

[52] M. W. N. Nijsten, C. E. Hack, M. Helle, H. J. Ten Duis, H. J. Klasen, and L. A. Aarden, "Interleukin-6 and its relation to the humoral immune response and clinical parameters in burned patients," *Surgery*, vol. 109, no. 6, pp. 761–767, 1991.

[53] D. A. Papanicolaou, R. L. Wilder, S. C. Manolagas, and G. P. Chrousos, "The pathophysiologic roles of interleukin-6 in human disease," *Annals of Internal Medicine*, vol. 128, no. 2, pp. 127–137, 1998.

[54] J. Y. Park and M. H. Pillinger, "Interleukin-6 in the pathogenesis of rheumatoid arthritis," *Bulletin of the NYU hospital for joint diseases*, vol. 65, supplement 1, pp. S4–S10, 2007.

[55] A. M. W. Petersen and B. K. Pedersen, "The anti-inflammatory effect of exercise," *Journal of Applied Physiology*, vol. 98, no. 4, pp. 1154–1162, 2005.

[56] J. Scheller and S. Rose-John, "Interleukin-6 and its receptor: from bench to bedside," *Medical Microbiology and Immunology*, vol. 195, no. 4, pp. 173–183, 2006.

[57] R. Schindler, J. Mancilla, S. Endres, R. Ghorbani, S. C. Clark, and C. A. Dinarello, "Correlations and interactions in the production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF," *Blood*, vol. 75, no. 1, pp. 40–47, 1990.

[58] A. Steensberg, C. P. Fischer, C. Keller, K. Møller, and B. K. Pedersen, "IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans," *American Journal of Physiology*, vol. 285, no. 2, pp. E433–E437, 2003.

[59] H. Tilg, C. A. Dinarello, and J. W. Mier, "IL-6 and APPs: anti-inflammatory and immunosuppressive mediators," *Immunology Today*, vol. 18, no. 9, pp. 428–432, 1997.

[60] H. Tilg, E. Trehu, M. B. Atkins, C. A. Dinarello, and J. W. Mier, "Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55," *Blood*, vol. 83, no. 1, pp. 113–118, 1994.

[61] T. van der Poll, M. Levi, C. E. Hack et al., "Elimination of interleukin 6 attenuates coagulation activation in experimental endotoxemia in chimpanzees," *Journal of Experimental Medicine*, vol. 179, no. 4, pp. 1253–1259, 1994.

[62] L. Z. Xiao, N. Topley, T. Ito, and A. Phillips, "Interleukin-6 regulation of transforming growth factor (TGF)-β receptor compartmentalization and turnover enhances TGF-β1 signaling," *The Journal of Biological Chemistry*, vol. 280, no. 13, pp. 12239–12245, 2005.

[63] M. Rincon, "Interleukin-6: from an inflammatory marker to a target for inflammatory diseases," *Trends in Immunology*, vol. 33, no. 11, pp. 571–577, 2012.

[64] R. Bonecchi, G. Bianchi, P. P. Bordignon et al., "Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s," *Journal of Experimental Medicine*, vol. 187, no. 1, pp. 129–134, 1998.

[65] J. Estaquier, T. Idziorek, W. Zou et al., "T helper type 1/T helper type 2 cytokines and T cell death: preventive effect of interleukin 12 on activation-induced and CD95 (FAS/APO-1)-mediated apoptosis of CD4+ T cells from human immunodeficiency virus-infected persons," *Journal of Experimental Medicine*, vol. 182, no. 6, pp. 1759–1767, 1995.

[66] P. Puccetti, M. L. Belladonna, and U. Grohmann, "Effects of IL-12 and IL-23 on antigen-presenting cells at the interface between innate and adaptive immunity," *Critical Reviews in Immunology*, vol. 22, no. 5-6, pp. 373–390, 2002.

[67] G. Trinchieri, "Interleukin-12 and the regulation of innate resistance and adaptive immunity," *Nature Reviews Immunology*, vol. 3, no. 2, pp. 133–146, 2003.

[68] U. Boehm, T. Klamp, M. Groot, and J. C. Howard, "Cellular responses to interferon-gamma," *Annual Review of Immunology*, vol. 15, pp. 749–795, 1997.

[69] T. Calandra, J.-D. Baumgartner, G. E. Grau et al., "Prognostic values of tumor necrosis factor/cachectin, interleukin-1, interferon-α, and interferon-γ in the serum of patients with septic shock," *Journal of Infectious Diseases*, vol. 161, no. 5, pp. 982–987, 1990.

[70] S. B. Flohé, H. Agrawal, S. Flohé, M. Rani, J. M. Bangen, and F. U. Schade, "Diversity of interferon γ and granulocyte-macrophage colony-stimulating factor in restoring immune dysfunction of dendritic cells and macrophages during polymicrobial sepsis," *Molecular Medicine*, vol. 14, no. 5-6, pp. 247–256, 2008.

[71] J. Leentjens, M. Kox, R. M. Koch et al., "Reversal of immunoparalysis in humans in vivo: a double-blind, placebo-controlled, randomized pilot study," *American Journal of Respiratory and Critical Care Medicine*, vol. 186, no. 9, pp. 838–845, 2012.

[72] H. Okamura, S. Kashiwamura, H. Tsutsui et al., "Regulation of interferon-gamma production by IL-12 and IL-18," *Current Opinion in Immunology*, vol. 10, no. 3, pp. 259–264, 1998.

[73] E. F. Wheelock, "Interferon-like virus-inhibitor induced in human leukocytes by phytohemagglutinin," *Science*, vol. 149, no. 3681, pp. 310–311, 1965.

[74] J. Bernhagen, T. Calandra, R. A. Mitchell et al., "MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia," *Nature*, vol. 365, no. 6448, pp. 756–759, 1993.

[75] J. Bernhagen, R. Krohn, H. Lue et al., "MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment," *Nature Medicine*, vol. 13, no. 5, pp. 587–596, 2007.

[76] R. Bucala and S. C. Donnelly, "Macrophage migration inhibitory factor: a probable link between inflammation and cancer," *Immunity*, vol. 26, no. 3, pp. 281–285, 2007.

[77] T. Calandra, J. Bernhagen, C. N. Metz et al., "MIF as a glucocorticoid-induced modulator of cytokine production," *Nature*, vol. 377, no. 6544, pp. 68–71, 1995.

[78] T. Calandra, J. Bernhagen, R. A. Mitchell, and R. Bucala, "The macrophage is an important and previously unrecognized source of macrophage migration inhibitory factor," *Journal of Experimental Medicine*, vol. 179, no. 6, pp. 1895–1902, 1994.

[79] T. Calandra, B. Echtenacher, D. Le Roy et al., "Protection from septic shock by neutralization of macrophage migration inhibitory factor," *Nature Medicine*, vol. 6, no. 2, pp. 164–170, 2000.

[80] T. Calandra and T. Roger, "Macrophage migration inhibitory factor: a regulator of innate immunity," *Nature Reviews Immunology*, vol. 3, no. 10, pp. 791–800, 2003.

[81] L. Leng, W. Wang, T. Roger et al., "Glucocorticoid-induced MIF expression by human CEM T cells," *Cytokine*, vol. 48, no. 3, pp. 177–185, 2009.

[82] M. Merk, R. A. Mitchell, S. Endres, and R. Bucala, "D-dopachrome tautomerase (D-DT or MIF-2): doubling the MIF cytokine family," *Cytokine*, vol. 59, no. 1, pp. 10–17, 2012.

[83] R. A. Mitchell, H. Liao, J. Chesney et al., "Macrophage migration inhibitory factor (MIF) sustains macrophage proinflammatory function by inhibiting p53: regulatory role in the innate immune response," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 1, pp. 345–350, 2002.

[84] T. Roger, A. Chanson, M. Knaup-Reymond, and T. Calandra, "Macrophage migration inhibitory factor promotes innate immune responses by suppressing glucocorticoid-induced expression of mitogen-activated protein kinase phosphatase-1," *European Journal of Immunology*, vol. 35, no. 12, pp. 3405–3413, 2005.

[85] R. D. W. Malefyt, J. Abrams, B. Bennett, C. G. Figdor, and J. E. de Vries, "Interleukin 10(IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes," *Journal of Experimental Medicine*, vol. 174, no. 5, pp. 1209–1220, 1991.

[86] D. F. Fiorentino, A. Zlotnik, T. R. Mosmann, M. Howard, and A. O'Garra, "IL-10 inhibits cytokine production by activated macrophages," *The Journal of Immunology*, vol. 147, no. 11, pp. 3815–3822, 1991.

[87] S. Q. Latifi, M. A. O'Riordan, and A. D. Levine, "Interleukin-10 controls the onset of irreversible septic shock," *Infection and Immunity*, vol. 70, no. 8, pp. 4441–4446, 2002.

[88] M. Seitz, P. Loetscher, B. Dewald, H. Towbin, H. Gallati, and M. Baggiolini, "Interleukin-10 differentially regulates cytokine inhibitor and chemokine release from blood mononuclear cells and fibroblasts," *European Journal of Immunology*, vol. 25, no. 4, pp. 1129–1132, 1995.

[89] G. C. Blobe, W. P. Schiemann, and H. F. Lodish, "Role of transforming growth factor β in human disease," *The New England Journal of Medicine*, vol. 342, no. 18, pp. 1350–1358, 2000.

[90] C. Bogdan and C. Nathan, "Modulation of macrophage function by transforming growth factor β, interleukin-4, and interleukin-10," *Annals of the New York Academy of Sciences*, vol. 685, pp. 713–739, 1993.

[91] C. Marie, J. M. Cavaillon, and M. R. Losser, "Elevated levels of circulating transforming growth factor-beta 1 in patients with the sepsis syndrome," *Annals of internal medicine*, vol. 125, no. 6, pp. 520–521, 1996.

[92] A. Pellacani, P. Wiesel, S. Razavi et al., "Down-regulation of high mobility group-I(Y) protein contributes to the inhibition of nitric-oxide synthase 2 by transforming growth factor-β1," *The Journal of Biological Chemistry*, vol. 276, no. 2, pp. 1653–1659, 2001.

[93] M. B. Sporn and A. B. Roberts, "Transforming growth factor-β: multiple actions and potential clinical applications," *Journal of the American Medical Association*, vol. 262, no. 7, pp. 938–941, 1989.

[94] M. Turner, D. Chantry, P. Katsikis, A. Berger, F. M. Brennan, and M. Feldmann, "Induction of the interleukin 1 receptor antagonist protein by transforming growth factor-β," *European Journal of Immunology*, vol. 21, no. 7, pp. 1635–1639, 1991.

[95] S. M. Opal and V. A. DePalo, "Anti-inflammatory cytokines," *Chest*, vol. 117, no. 4, pp. 1162–1172, 2000.

[96] R. A. Seder, W. E. Paul, M. M. Davis, and B. F. de st. Groth, "The presence of interleukin 4 during in vitro priming determines the lymphokine-producing potential of CD4+ T cells from T cell receptor transgenic mice," *Journal of Experimental Medicine*, vol. 176, no. 4, pp. 1091–1098, 1992.

[97] J.-M. Cavaillon, C. Munoz, C. Fitting, B. Misset, and J. Carlet, "Circulating cytokines: the tip of the iceberg?" *Circulatory Shock*, vol. 38, no. 2, pp. 145–152, 1992.

[98] T. S. Blackwell and J. W. Christman, "Sepsis and cytokines: current status," *British Journal of Anaesthesia*, vol. 77, no. 1, pp. 110–117, 1996.

[99] N. Aikawa, "Cytokine storm in the pathogenesis of multiple organ dysfunction syndrome associated with surgical insults," *Nippon Geka Gakkai Zasshi*, vol. 97, no. 9, pp. 771–777, 1996.

[100] W. G. Junger, D. B. Hoyt, F. C. Liu, W. H. Loomis, and R. Coimbra, "Immunosuppression after endotoxin shock: the result of multiple anti-inflammatory factors," *Journal of Trauma*, vol. 40, no. 5, pp. 702–709, 1996.

[101] B. M. Tang, S. J. Huang, and A. S. McLean, "Genome-wide transcription profiling of human sepsis: a systematic review," *Critical Care*, vol. 14, no. 6, article R237, 2010.

[102] C. E. Hack, L. A. Aarden, and L. G. Thijs, "Role of cytokines in sepsis," *Advances in Immunology*, vol. 66, pp. 101–195, 1997.

[103] T. van der Poll and S. J. H. van Deventer, "Cytokines and anticytokines in the pathogenesis of sepsis," *Infectious Disease Clinics of North America*, vol. 13, no. 2, pp. 413–426, 1999.

[104] C. Dinarello, W. Arend, J. Sims et al., "IL-1 family nomenclature," *Nature Immunology*, vol. 11, no. 11, article 973, 2010.

[105] M. Kapoor, J. Martel-Pelletier, D. Lajeunesse, J. Pelletier, and H. Fahmi, "Role of proinflammatory cytokines in the pathophysiology of osteoarthritis," *Nature Reviews Rheumatology*, vol. 7, no. 1, pp. 33–42, 2011.

[106] M. Lewis, L. A. Tartaglia, A. Lee et al., "Cloning and expression of cDNAs for two distinct murine tumor necrosis factor receptors demonstrate one receptor is species specific," *Proceedings of*

the National Academy of Sciences of the United States of America, vol. 88, no. 7, pp. 2830–2834, 1991.

[107] M. Bhatia and S. Moochhala, "Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome," *Journal of Pathology*, vol. 202, no. 2, pp. 145–156, 2004.

[108] P. Selby, S. Hobbs, C. Viner et al., "Tumour necrosis factor in man: clinical and biological observations," *British Journal of Cancer*, vol. 56, no. 6, pp. 803–808, 1987.

[109] M. L. Sherman, D. R. Spriggs, K. A. Arthur, K. Imamura, E. Frei III, and D. W. Kufe, "Recombinant human tumor necrosis factor administered as a five-day continuous infusion in cancer patients: phase I toxicity and effects on lipid metabolism," *Journal of Clinical Oncology*, vol. 6, no. 2, pp. 344–350, 1988.

[110] T. van der Poll, H. R. Buller, H. ten Cate et al., "Activation of coagulation after administration of tumor necrosis factor to normal subjects," *The New England Journal of Medicine*, vol. 322, no. 23, pp. 1622–1627, 1990.

[111] A. Tewari, W. C. Buhles Jr., and H. F. Starnes Jr., "Preliminary report: effects of interleukin-1 on platelet counts," *The Lancet*, vol. 336, no. 8717, pp. 712–714, 1990.

[112] C. A. Dinarello, "Interleukin-1 and interleukin-1 antagonism," *Blood*, vol. 77, no. 8, pp. 1627–1652, 1991.

[113] S. Okusawa, J. A. Gelfand, T. Ikejima, R. J. Connolly, and C. A. DInarello, "Interleukin 1 induces a shock-like state in rabbits. Synergism with tumor necrosis factor and the effect of cyclooxygenase inhibition," *The Journal of Clinical Investigation*, vol. 81, no. 4, pp. 1162–1172, 1988.

[114] J. G. Cannon, R. G. Tompkins, J. A. Gelfand et al., "Circulating interleukin-1 and tumor necrosis factor in septic shock and experimental endotoxin fever," *Journal of Infectious Diseases*, vol. 161, no. 1, pp. 79–84, 1990.

[115] D. G. Hesse, K. J. Tracey, Y. Fong et al., "Cytokine appearance in human endotoxemia and primate bacteremia," *Surgery Gynecology and Obstetrics*, vol. 166, no. 2, pp. 147–153, 1988.

[116] H. R. Michie, K. R. Manogue, D. R. Spriggs et al., "Detection of circulating tumor necrosis factor after endotoxin administration," *The New England Journal of Medicine*, vol. 318, no. 23, pp. 1481–1486, 1988.

[117] A. F. Suffredini, R. E. Fromm, M. M. Parker et al., "The cardiovascular response of normal humans to the administration of endotoxin," *The New England Journal of Medicine*, vol. 321, no. 5, pp. 280–287, 1989.

[118] C. Fahlman, F. W. Jacobsen, O. P. Veiby, I. K. McNiece, H. K. Blomhoff, and S. E. W. Jacobsen, "Tumor necrosis factor-α (TNF-α) potently enhances in vitro macrophage production from primitive murine hematopoietic progenitor cells in combination with stem cell factor and interleukin-7: novel stimulatory role of p55 TNF receptors," *Blood*, vol. 84, no. 5, pp. 1528–1533, 1994.

[119] D. Conte, M. Holcik, C. A. Lefebvre et al., "Inhibitor of apoptosis protein cIAP2 is essential for lipopolysaccharide-induced macrophage survival," *Molecular and Cellular Biology*, vol. 26, no. 2, pp. 699–708, 2006.

[120] H. Nakae, S. Endo, K. Inada, T. Takakuwa, and T. Kasai, "Changes in adhesion molecule levels in sepsis," *Research Communications in Molecular Pathology and Pharmacology*, vol. 91, no. 3, pp. 329–338, 1996.

[121] M. Shimaoka and E. J. Park, "Advances in understanding sepsis," *European Journal of Anaesthesiology*, vol. 25, no. 42, pp. 146–153, 2008.

[122] G. A. Spinas, U. Keller, and M. Brockhaus, "Release of soluble receptors for tumor necrosis factor (TNF) in relation to circulating TNF during experimental endotoxinemia," *The Journal of Clinical Investigation*, vol. 90, no. 2, pp. 533–536, 1992.

[123] D. B. Kuhns, W. G. Alvord, and J. I. Gallin, "Increased circulating cytokines, cytokine antagonists, and E-selectin after intravenous administration of endotoxin in humans," *Journal of Infectious Diseases*, vol. 171, no. 1, pp. 145–152, 1995.

[124] W. Ertel, F. A. Scholl, H. Gallati et al., "Increased release of soluble tumor necrosis factor receptors into blood during clinical sepsis," *Archives of Surgery*, vol. 129, no. 12, pp. 1330–1337, 1994.

[125] B. Gardlund, J. Sjolin, A. Nilsson, M. Roll, C.-J. Wickerts, and B. Wretlind, "Plasma levels of cytokines in primary septic shock in humans: correlation with disease severity," *Journal of Infectious Diseases*, vol. 172, no. 1, pp. 296–301, 1995.

[126] A. S. Goldie, K. C. H. Fearon, J. A. Ross et al., "Natural cytokine antagonists and endogenous antiendotoxin core antibodies in sepsis syndrome," *Journal of the American Medical Association*, vol. 274, no. 2, pp. 172–177, 1995.

[127] E. Fischer, M. A. Marano, K. J. Van Zee et al., "Interleukin-1 receptor blockade improves survival and hemodynamic performance in *Escherichia coli* septic shock, but fails to alter host responses to sublethal endotoxemia," *The Journal of Clinical Investigation*, vol. 89, no. 5, pp. 1551–1557, 1992.

[128] A. A. Creasey, P. Stevens, J. Kenney et al., "Endotoxin and cytokine profile in plasma of baboons challenged with lethal and sublethal *Escherichia coli*," *Circulatory Shock*, vol. 33, no. 2, pp. 84–91, 1991.

[129] P. Damas, D. Ledoux, M. Nys et al., "Cytokine serum level during severe sepsis in human IL-6 as a marker of severity," *Annals of Surgery*, vol. 215, no. 4, pp. 356–362, 1992.

[130] A. M. Cruickshank, W. D. Fraser, H. J. G. Burns, J. van Damme, and A. Shenkin, "Response of serum interleukin-6 in patients undergoing elective surgery of varying severity," *Clinical Science*, vol. 79, no. 2, pp. 161–165, 1990.

[131] R. C. Hoch, R. Rodriguez, T. Manning et al., "Effects of accidental trauma on cytokine and endotoxin production," *Critical Care Medicine*, vol. 21, no. 6, pp. 839–845, 1993.

[132] C. E. Hack, E. R. De Groot, R. J. F. Felt-Bersma et al., "Increased plasma levels of interleukin-6 in sepsis," *Blood*, vol. 74, no. 5, pp. 1704–1710, 1989.

[133] E. Borrelli, P. Roux-Lombard, G. E. Grau et al., "Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk," *Critical Care Medicine*, vol. 24, no. 3, pp. 392–397, 1996.

[134] A. Waage, P. Brandtzaeg, A. Halstensen, P. Kierulf, and T. Espevik, "The complex pattern of cytokines in serum from patients with meningococcal septic shock. Association between interleukin 6, interleukin 1, and fatal outcome," *Journal of Experimental Medicine*, vol. 169, no. 1, pp. 333–338, 1989.

[135] J. Preiser, D. Schmartz, P. van der Linden et al., "Interleukin-6 administration has no acute hemodynamic or hematologic effect in the dog," *Cytokine*, vol. 3, no. 1, pp. 1–4, 1991.

[136] I. Kushner and D. L. Rzewnicki, "The acute phase response: general aspects," *Bailliere's Clinical Rheumatology*, vol. 8, no. 3, pp. 513–530, 1994.

[137] S. Cuzzocrea, L. Sautebin, G. De Sarro et al., "Role of IL-6 in the pleurisy and lung injury caused by carrageenan," *The Journal of Immunology*, vol. 163, no. 9, pp. 5094–5104, 1999.

[138] S. Cuzzocrea, G. De Sarro, G. Costantino et al., "Role of interleukin-6 in a non-septic shock model induced by zymosan," *European Cytokine Network*, vol. 10, no. 2, pp. 191–203, 1999.

[139] N. Pathan, C. A. Hemingway, A. A. Alizadeh et al., "Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock," *The Lancet*, vol. 363, no. 9404, pp. 203–209, 2004.

[140] K. Yoshizawa, M. Naruto, and N. Ida, "Injection time of interleukin-6 determines fatal outcome in experimental endotoxin shock," *Journal of Interferon and Cytokine Research*, vol. 16, no. 12, pp. 995–1000, 1996.

[141] Z. Xing, J. Gauldie, G. Cox et al., "IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses," *The Journal of Clinical Investigation*, vol. 101, no. 2, pp. 311–320, 1998.

[142] D. G. Remick, G. Bolgos, S. Copeland, and J. Siddiqui, "Role of interleukin-6 in mortality from and physiologic response to sepsis," *Infection and Immunity*, vol. 73, no. 5, pp. 2751–2757, 2005.

[143] L. L. Jones and D. A. A. Vignali, "Molecular interactions within the IL-6/IL-12 cytokine/receptor superfamily," *Immunologic Research*, vol. 51, no. 1, pp. 5–14, 2011.

[144] M. L. Steinhauser, C. M. Hogaboam, N. W. Lukacs, R. M. Strieter, and S. L. Kunkel, "Multiple roles for IL-12 in a model of acute septic peritonitis," *The Journal of Immunology*, vol. 162, no. 9, pp. 5437–5443, 1999.

[145] D. A. Zisman, S. L. Kunkel, R. M. Strieter et al., "Anti-interleukin-12 therapy protects mice in lethal endotoxemia but impairs bacterial clearance in murine *Escherichia coli* peritoneal sepsis," *Shock*, vol. 8, no. 5, pp. 349–356, 1997.

[146] P. M. Jansen, T. C. T. M. V. Kraan, I. W. de Jong et al., "Release of interleukin-12 in experimental *Escherichia coli* septic shock in baboons: relation to plasma levels of interleukin-10 and interferon-γ," *Blood*, vol. 87, no. 12, pp. 5144–5151, 1996.

[147] S. E. Moreno, J. C. Alves-Filho, T. M. Alfaya, J. S. da Silva, S. H. Ferreira, and F. Y. Liew, "IL-12, but not IL-18, is critical to neutrophil activation and resistance to polymicrobial sepsis induced by cecal ligation and puncture," *The Journal of Immunology*, vol. 177, no. 5, pp. 3218–3224, 2006.

[148] H. Weighardt, C. Heidecke, A. Westerholt et al., "Impaired monocyte IL-12 production before surgery as a predictive factor for the lethal outcome of postoperative sepsis," *Annals of Surgery*, vol. 235, no. 4, pp. 560–567, 2002.

[149] S. A. Stanilova, Z. T. Karakolev, G. S. Dimov et al., "High interleukin 12 and low interleukin 10 production after in vitro stimulation detected in sepsis survivors," *Intensive Care Medicine*, vol. 31, no. 3, pp. 401–407, 2005.

[150] H. Wu, C. Shih, C. Lin, C. Hua, and D. Chuang, "Serial increase of IL-12 response and human leukocyte antigen-DR expression in severe sepsis survivors," *Critical Care*, vol. 15, no. 5, article R224, 2011.

[151] Z. Wang, S. L. Reiner, S. Zheng, D. K. Dalton, and R. M. Locksley, "CD4+ effector cells default to the Th2 pathway in interferon γ-deficient mice infected with Leishmania major," *Journal of Experimental Medicine*, vol. 179, no. 4, pp. 1367–1371, 1994.

[152] S. Huang, W. Hendriks, A. Althage et al., "Immune response in mice that lack the interferon-γ receptor," *Science*, vol. 259, no. 5102, pp. 1742–1745, 1993.

[153] A. M. Cooper, D. K. Dalton, T. A. Stewart, J. P. Griffin, D. G. Russell, and I. M. Orme, "Disseminated tuberculosis in interferon γ gene-disrupted mice," *Journal of Experimental Medicine*, vol. 178, no. 6, pp. 2243–2247, 1993.

[154] U. Müller, U. Steinhoff, L. F. L. Reis et al., "Functional role of type I and type II interferons in antiviral defense," *Science*, vol. 264, no. 5167, pp. 1918–1921, 1994.

[155] F. P. Heinzel, "The role of IFN-γ in the pathology of experimental endotoxemia," *The Journal of Immunology*, vol. 145, no. 9, pp. 2920–2924, 1990.

[156] B. D. Car, V. M. Eng, B. Schnyder et al., "Interferon γ receptor deficient mice are resistant to endotoxic shock," *Journal of Experimental Medicine*, vol. 179, no. 5, pp. 1437–1444, 1994.

[157] C. Munoz, J. Carlet, C. Fitting, B. Misset, J.-P. Bleriot, and J.-M. Cavaillon, "Dysregulation of in vitro cytokine production by monocytes during sepsis," *The Journal of Clinical Investigation*, vol. 88, no. 5, pp. 1747–1754, 1991.

[158] N. R. Ferguson, H. F. Galley, and N. R. Webster, "T helper cell subset ratios in patients with severe sepsis," *Intensive Care Medicine*, vol. 25, no. 1, pp. 106–109, 1999.

[159] A. R. Rich and M. R. Lewis, "The nature of allergy in tuberculosis as revealed by tissue culture studies," *Bulletin of the Johns Hopkins Hospital*, vol. 50, pp. 115–131, 1932.

[160] T. Calandra, L. A. Spiegel, C. N. Metz, and R. Bucala, "Macrophage migration inhibitory factor is a critical mediator of the activation of immune cells by exotoxins of Gram-positive bacteria," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 19, pp. 11383–11388, 1998.

[161] M. Merk, J. Baugh, S. Zierow et al., "The Golgi-associated protein p115 mediates the secretion of macrophage migration inhibitory factor," *The Journal of Immunology*, vol. 182, no. 11, pp. 6896–6906, 2009.

[162] T. Roger, J. David, M. P. Glauser, and T. Calandra, "MIF regulates innate immune responses through modulation of Toll-like receptor 4," *Nature*, vol. 414, no. 6866, pp. 920–924, 2001.

[163] X. Shi, L. Leng, T. Wang et al., "CD44 is the signaling component of the macrophage migration inhibitory factor-CD74 receptor complex," *Immunity*, vol. 25, no. 4, pp. 595–606, 2006.

[164] L. Leng, C. N. Metz, Y. Fang et al., "MIF signal transduction initiated by binding to CD74," *Journal of Experimental Medicine*, vol. 197, no. 11, pp. 1467–1476, 2003.

[165] A. G. Rossi, C. Haslett, N. Hirani et al., "Human circulating eosinophils secrete macrophage migration inhibitory factor (MIF): potential role in asthma," *The Journal of Clinical Investigation*, vol. 101, no. 12, pp. 2869–2874, 1998.

[166] A. Mikulowska, C. N. Metz, R. Bucala, and R. Holmdahl, "Macrophage migration inhibitory factor is involved in the pathogenesis of collagen type II-lnduced arthritis in mice," *The Journal of Immunology*, vol. 158, no. 11, pp. 5514–5517, 1997.

[167] S. Lin, X. Yu, Y. Chen et al., "De novo expression of macrophage migration inhibitory factor in atherogenesis in rabbits," *Circulation Research*, vol. 87, no. 12, pp. 1202–1208, 2000.

[168] Y. P. de Jong, A. C. Abadia-Molina, A. R. Satoskar et al., "Development of chronic colitis is dependent on the cytokine MIF," *Nature Immunology*, vol. 2, no. 11, pp. 1061–1066, 2001.

[169] Y. Al-Abed, D. Dabideen, B. Aljabari et al., "ISO-1 binding to the tautomerase active site of MIF inhibits its pro-inflammatory activity and increases survival in severe sepsis," *The Journal of Biological Chemistry*, vol. 280, no. 44, pp. 36541–36544, 2005.

[170] M. Bozza, A. R. Satoskar, G. Lin et al., "Targeted disruption of migration inhibitory factor gene reveals its critical role in sepsis," *Journal of Experimental Medicine*, vol. 189, no. 2, pp. 341–346, 1999.

[171] N. Matsuda, J. Nishihira, Y. Takahashi, O. Kemmotsu, and Y. Hattori, "Role of macrophage migration inhibitory factor in acute lung injury in mice with acute pancreatitis complicated by endotoxemia," *American Journal of Respiratory Cell and Molecular Biology*, vol. 35, no. 2, pp. 198–205, 2006.

[172] S. Kobayashi, J. Nishihira, S. Watanabe, and S. Todo, "Prevention of lethal acute hepatic failure by antimacrophage migration inhibitory factor antibody in mice treated with bacille Calmette-Guerin and lipopolysaccharide," *Hepatology*, vol. 29, no. 6, pp. 1752–1759, 1999.

[173] L. B. Garner, M. S. Willis, D. L. Carlson et al., "Macrophage migration inhibitory factor is a cardiac-derived myocardial depressant factor," *American Journal of Physiology*, vol. 285, no. 6, pp. H2500–H2509, 2003.

[174] E. J. Miller, J. Li, L. Leng et al., "Macrophage migration inhibitory factor stimulates AMP-activated protein kinase in the ischaemic heart," *Nature*, vol. 451, no. 7178, pp. 578–582, 2008.

[175] M. Merk, S. Zierow, L. Leng et al., "The D-dopachrome tautomerase (DDT) gene product is a cytokine and functional homolog of macrophage migration inhibitory factor (MIF)," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 34, pp. E577–E585, 2011.

[176] A. Beishuizen, L. G. Thijs, C. Haanen, and I. Vermes, "Macrophage migration inhibitory factor and hypothalamo-pituitary-adrenal function during critical illness," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 6, pp. 2811–2816, 2001.

[177] T. Brenner, S. Hofer, C. Rosenhagen et al., "Macrophage migration inhibitory factor (MIF) and manganese superoxide dismutase (MnSOD) as early predictors for survival in patients with severe sepsis or septic shock," *Journal of Surgical Research*, vol. 164, no. 1, pp. e163–e171, 2010.

[178] S. Yende, D. C. Angus, L. Kong et al., "The influence of macrophage migration inhibitory factor gene polymorphisms on outcome from community-acquired pneumonia," *The FASEB Journal*, vol. 23, no. 8, pp. 2403–2411, 2009.

[179] P. Renner, T. Roger, P. Bochud et al., "A functional microsatellite of the macrophage migration inhibitory factor gene associated with meningococcal disease," *The FASEB Journal*, vol. 26, no. 2, pp. 907–916, 2012.

[180] S. Doernberg, B. Schaaf, K. Dalhoff et al., "Association of macrophage migration inhibitory factor (MIF) polymorphisms with risk of meningitis from *Streptococcus pneumoniae*," *Cytokine*, vol. 53, no. 3, pp. 292–294, 2011.

[181] G. A. Awandare, J. J. Martinson, T. Were et al., "MIF (Macrophage Migration Inhibitory Factor) promoter polymorphisms and susceptibility to severe malarial anemia," *Journal of Infectious Diseases*, vol. 200, no. 4, pp. 629–637, 2009.

[182] M. Howard, T. Muchamuel, S. Andrade, and S. Menon, "Interleukin 10 protects mice from lethal endotoxemia," *Journal of Experimental Medicine*, vol. 177, no. 4, pp. 1205–1208, 1993.

[183] M. Howard and A. O'Garra, "Biological properties of interleukin 10," *Journal of Clinical Immunology*, vol. 12, no. 4, pp. 239–247, 1992.

[184] G. Y. Song, C. Chung, I. H. Chaudry, and A. Ayala, "What is the role of interleukin 10 in polymicrobial sepsis: anti-inflammatory agent or immunosuppressant?" *Surgery*, vol. 126, no. 2, pp. 378–383, 1999.

[185] T. van der Poll, A. Marchant, W. A. Buurman et al., "Endogenous IL-10 protects mice from death during septic peritonitis," *The Journal of Immunology*, vol. 155, no. 11, pp. 5397–5401, 1995.

[186] L. Zeng, W. Gu, K. Chen et al., "Clinical relevance of the interleukin 10 promoter polymorphisms in Chinese Han patients with major trauma: genetic association studies," *Critical Care*, vol. 13, no. 6, article R188, 2009.

[187] K. M. Gilbert, M. Thoman, K. Bauche, T. Pham, and W. O. Weigle, "Transforming growth factor-β1 induces antigen-specific unresponsiveness in naive T cells," *Immunological Investigations*, vol. 26, no. 4, pp. 459–472, 1997.

[188] Y. Y. Wan and R. A. Flavell, "TGF-β and regulatory T cell in immunity and autoimmunity," *Journal of Clinical Immunology*, vol. 28, no. 6, pp. 647–659, 2008.

[189] F. Randow, U. Syrbe, C. Meisel et al., "Mechanism of endotoxin desensitization: involvement of interleukin 10 and transforming growth factor β," *Journal of Experimental Medicine*, vol. 181, no. 5, pp. 1887–1892, 1995.

[190] M. A. Perrella, C. M. Hsieh, W. S. Lee et al., "Arrest of endotoxin-induced hypotension by transforming growth factor beta1," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 5, pp. 2054–2059, 1996.

[191] B. S. Pender, "Transforming growth factor β1 alters rat peritoneal macrophage mediator production and improves survival during endotoxic shock," *European Cytokine Network*, vol. 7, no. 2, pp. 137–142, 1996.

[192] S. Zanotti, A. Kumar, and A. Kumar, "Cytokine modulation in sepsis and septic shock," *Expert Opinion on Investigational Drugs*, vol. 11, no. 8, pp. 1061–1075, 2002.

[193] S. Knapp, F. Thalhammer, G. J. Locker et al., "Prognostic value of MIP-1α, TGF-β2, sELAM-1, and sVCAM-1 in patients with gram-positive sepsis," *Clinical Immunology and Immunopathology*, vol. 87, no. 2, pp. 139–144, 1998.

[194] A. Kumar, A. Kumar, B. Paladugu, J. Mensing, and J. E. Parrillo, "Transforming growth factor-β1 blocks in vitro cardiac myocyte depression induced by tumor necrosis factor-α, interleukin-1β, and human septic shock serum," *Critical Care Medicine*, vol. 35, no. 2, pp. 358–364, 2007.

[195] J. Zamorano, H. Y. Wang, L. Wang, J. H. Pierce, and A. D. Keegan, "IL-4 protects cells from apoptosis via the insulin receptor substrate pathway and a second independent signaling pathway," *The Journal of Immunology*, vol. 157, no. 11, pp. 4926–4934, 1996.

[196] M. Yanagida, H. Fukamachi, K. Ohgami et al., "Effects of T-helper 2-type cytokines, interleukin-3 (IL-3), IL-4, IL-5, and IL-6 on the survival of cultured human mast cells," *Blood*, vol. 86, no. 10, pp. 3705–3714, 1995.

[197] M. B. Lutz, M. Schnare, M. Menges et al., "Differential functions of IL-4 receptor types I and II for dendritic cell maturation and IL-12 production and their dependency on GM-CSF," *The Journal of Immunology*, vol. 169, no. 7, pp. 3574–3580, 2002.

[198] J. M. Baumhofer, B. G. Beinhauer, J. E. Wang et al., "Gene transfer with IL-4 and IL-13 improves survival in lethal endotoxemia in the mouse and ameliorates peritoneal macrophages immune competence," *European Journal of Immunology*, vol. 28, no. 2, pp. 610–615, 1998.

[199] O. Hultgren, M. Kopf, and A. Tarkowski, "Outcome of *Staphylococcus aureus*-triggered sepsis and arthritis in IL-4-deficient mice depends on the genetic background of the host," *European Journal of Immunology*, vol. 29, no. 8, pp. 2400–2405, 1999.

[200] H. P. Wu, C. L. Wu, C. K. Chen et al., "The interleukin-4 expression in patients with severe sepsis," *Journal of Critical Care*, vol. 23, no. 4, pp. 519–524, 2008.

[201] W. Gu, L. Zeng, L. Zhang et al., "Association of interleukin 4-589T/C Polymorphism with TH1 and TH2 bias and sepsis in

chinese major trauma patients," *Journal of Trauma*, vol. 71, no. 6, pp. 1583–1587, 2011.

[202] C. J. Fisher Jr., S. M. Opal, J. F. Dhainaut et al., "Influence of an anti-tumor necrosis factor monoclonal antibody on cytokine levels in patients with sepsis. The CB0006 Sepsis Syndrome Study Group," *Critical Care Medicine*, vol. 21, no. 3, pp. 318–327, 1993.

[203] S. M. Opal, C. J. Fisher Jr., J. A. Dhainaut et al., "Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial," *Critical Care Medicine*, vol. 25, no. 7, pp. 1115–1124, 1997.

[204] F. Zeni, B. Freeman, and C. Natanson, "Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment," *Critical Care Medicine*, vol. 25, no. 7, pp. 1095–1100, 1997.

[205] J. Cohen and J. Carlet, "INTERSEPT: an international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-α in patients with sepsis," *Critical Care Medicine*, vol. 24, no. 9, pp. 1431–1440, 1996.

[206] W. R. Parrish, M. Gallowitsch-Puerta, C. J. Czura, and K. J. Tracey, "Experimental therapeutic strategies for severe sepsis: mediators and mechanisms," *Annals of the New York Academy of Sciences*, vol. 1144, pp. 210–236, 2008.

[207] L. Ulloa and K. J. Tracey, "The "cytokine profile": a code for sepsis," *Trends in Molecular Medicine*, vol. 11, no. 2, pp. 56–63, 2005.

[208] J. B. Lubetsky, A. Dios, J. Han et al., "The tautomerase active site of macrophage migration inhibitory factor is a potential target for discovery of novel anti-inflammatory agents," *The Journal of Biological Chemistry*, vol. 277, no. 28, pp. 24976–24982, 2002.

[209] L. Leng, L. Chen, J. Fan et al., "A small-molecule macrophage migration inhibitory factor antagonist protects against glomerulonephritis in Lupus-Prone NZB/NZW F1 and MRL/lpr mice," *The Journal of Immunology*, vol. 186, no. 1, pp. 527–538, 2011.

[210] A. Arjona, H. G. Foellmer, T. Town et al., "Abrogation of macrophage migration inhibitory factor decreases West Nile virus lethality by limiting viral neuroinvasion," *The Journal of Clinical Investigation*, vol. 117, no. 10, pp. 3059–3066, 2007.

[211] R. J. Kerschbaumer, M. Rieger, D. Völkel et al., "Neutralization of macrophage migration inhibitory factor (MIF) by fully human antibodies correlates with their specificity for the β-sheet structure of MIF," *The Journal of Biological Chemistry*, vol. 287, no. 10, pp. 7446–7455, 2012.

[212] A. A. Hare, L. Leng, S. Gandavadi et al., "Optimization of N-benzyl-benzoxazol-2-ones as receptor antagonists of macrophage migration inhibitory factor (MIF)," *Bioorganic and Medicinal Chemistry Letters*, vol. 20, no. 19, pp. 5811–5814, 2010.

[213] S. Kraemer, H. Lue, A. Zernecke et al., "MIF-chemokine receptor interactions in atherogenesis are dependent on an N-loop-based 2-site binding mechanism," *The FASEB Journal*, vol. 25, no. 3, pp. 894–906, 2011.

[214] J. J. Presneill, T. Harris, A. G. Stewart, J. F. Cade, and J. W. Wilson, "A randomized phase II trial of granulocyte-macrophage colony-stimulating factor therapy in severe sepsis with respiratory dysfunction," *American Journal of Respiratory and Critical Care Medicine*, vol. 166, no. 2, pp. 138–143, 2002.

[215] A. J. Rosenbloom, P. K. Linden, A. Dorrance, N. Penkosky, M. H. Cohen-Melamed, and M. R. Pinsky, "Effect of granulocyte-monocyte colony-stimulating factor therapy on leukocyte function and clearance of serious infection in nonneutropenic patients," *Chest*, vol. 127, no. 6, pp. 2139–2150, 2005.

[216] H. C. Polk Jr., W. G. Cheadle, D. H. Livingston et al., "A randomized prospective clinical trial to determine the efficacy of interferon-γ in severely injured patients," *American Journal of Surgery*, vol. 163, no. 2, pp. 191–196, 1992.

[217] C. T. Esmon, "The interactions between inflammation and coagulation," *British Journal of Haematology*, vol. 131, no. 4, pp. 417–430, 2005.

[218] C. T. Esmon, "The protein C pathway," *Chest*, vol. 124, supplement 3, pp. 26S–32S, 2003.

[219] A. P. Neyrinck, K. D. Liu, J. P. Howard, and M. A. Matthay, "Protective mechanisms of activated protein C in severe inflammatory disorders," *British Journal of Pharmacology*, vol. 158, no. 4, pp. 1034–1047, 2009.

[220] P. L. Vera, T. E. Wolfe, A. E. Braley, and K. L. Meyer-Siegler, "Thrombin induces macrophage migration inhibitory factor release and upregulation in urothelium: a possible contribution to bladder inflammation," *PLoS ONE*, vol. 5, no. 12, Article ID e15904, 2010.

[221] H. F. Galley, N. E. El Sakka, N. R. Webster, D. A. Lowes, and B. H. Cuthbertson, "Activated protein C inhibits chemotaxis and interleukin-6 release by human neutrophils without affecting other neutrophil functions," *British Journal of Anaesthesia*, vol. 100, no. 6, pp. 815–819, 2008.

[222] K. Okajima, "Regulation of inflammatory responses by natural anticoagulants," *Immunological Reviews*, vol. 184, pp. 258–274, 2001.

[223] M. Schmidt-Supprian, C. Murphy, B. White et al., "Activated protein C inhibits tumor necrosis factor and macrophage migration inhibitory factor production in monocytes," *European Cytokine Network*, vol. 11, no. 3, pp. 407–413, 2000.

[224] P. Bilbault, T. Lavaux, A. Launoy et al., "Influence of drotrecogin alpha (activated) infusion on the variation of Bax/Bcl-2 and Bax/Bcl-xl ratios in circulating mononuclear cells: a cohort study in septic shock patients," *Critical Care Medicine*, vol. 35, no. 1, pp. 69–75, 2007.

[225] F. P. da Silva and V. Nizet, "Cell death during sepsis: integration of disintegration in the inflammatory response to overwhelming infection," *Apoptosis*, vol. 14, no. 4, pp. 509–521, 2009.

[226] F. B. Taylor Jr., A. Chang, and C. T. Esmon, "Protein C prevents the coagulopathic and lethal effects of *Escherichia coli* infusion in the baboon," *The Journal of Clinical Investigation*, vol. 79, no. 3, pp. 918–925, 1987.

[227] G. R. Bernard, E. W. Ely, T. J. Wright et al., "Safety and dose relationship of recombinant human activated protein C for coagulopathy in severe sepsis," *Critical Care Medicine*, vol. 29, no. 11, pp. 2051–2059, 2001.

[228] G. R. Bernard, J. Vincent, P. Laterre et al., "Efficacy and safety of recombinant human activated protein C for severe sepsis," *The New England Journal of Medicine*, vol. 344, no. 10, pp. 699–709, 2001.

[229] R. P. Dellinger, M. M. Levy, J. M. Carlet et al., "Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008," *Critical Care Medicine*, vol. 36, no. 1, pp. 296–327, 2008.

[230] V. M. Ranieri, B. T. Thompson, P. S. Barie et al., "Drotrecogin alfa (activated) in adults with septic shock," *The New England Journal of Medicine*, vol. 366, no. 22, pp. 2055–2064, 2012.