Sepsis and cytokines: current status

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Sepsis syndrome represents a spectrum of pathophysiology that results from an exuberant host inflammatory response to a specific inciting event. The clinical course of sepsis syndrome ranges from mild physiological derangements to severe multiple organ dysfunction and death. In the United States, the incidence of sepsis syndrome has been estimated at 400,000 cases annually, with a fatality rate of nearly 40%. The development of sepsis syndrome is related to a complex interplay of lipid, protein and possibly carbohydrate mediators. Although a large variety of mediators have been implicated in the development of sepsis syndrome, a rapidly growing body of experimental evidence suggests that proteins belonging to the cytokine family are decisive factors in determining the pathobiology of sepsis syndrome. This article reviews recent information which demonstrates the role of cytokines in the development of sepsis syndrome. Since cytokines play critical roles in the initiation and perpetuation of sepsis syndrome, we also review interventions which abrogate the actions of cytokines and might be effective treatments for sepsis syndrome and related disorders.

**Sepsis syndrome**

A consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine in 1991 proposed standardized terminology to define various aspects of sepsis syndrome [2]. These definitions stress the concept that the development of sepsis syndrome is related to a systemic inflammatory host response to an inciting event. The Consensus Conference recommended systemic inflammatory response syndrome (SIRS) as an umbrella term. SIRS is recognized by a constellation of cardinal signs which include tachypnoea, fever or hypothermia, tachycardia and leucocytosis or leucopenia with a “left shifted” differential white blood cell count. SIRS can result from either infectious or non-infectious conditions. Non-infectious conditions which are associated with SIRS include trauma, burns, haemorrhagic or hypovolaemic shock and pancreatitis. Sepsis is defined as SIRS which results from infection, which can be bacterial, paracystic, protozoan or viral. Although most cases of sepsis are related to Gram-negative infections, full blown sepsis can result from Gram-positive infections.

The severity of sepsis is proportional to the intensity of the host response. Severe sepsis is defined as sepsis which is associated with specific or multiple organ dysfunction. Septic shock occurs when there is systemic hypotension that is associated with tissue hypoperfusion and anaerobic metabolism. This simple classification system has been shown to predict mortality in a stepwise manner with a mortality of SIRS of 7%, sepsis of 16%, severe sepsis of 20% and septic shock of 46% [45]. This stratification of sepsis syndrome appears to reflect a continuum of systemic inflammation with increasing inflammation being associated with worsening clinical severity.

**Cytokine hypothesis**

Cytokines are a group of small signalling proteins produced by a large variety of cells that are thought to be important for host defence, wound healing and other essential host functions. Although cytokines are important for these homeostatic functions, excessive production and release of cytokines initiate widespread tissue injury which can result in organ dysfunction. Sepsis syndrome seems to result from overwhelming systemic inflammation which is caused by excessive release of cytokines into the systemic circulation.

The recent development of precise molecular tools for identifying and measuring cytokines has led to rapid accumulation of data implicating cytokines in the pathobiology of sepsis syndrome. Four cytokines, tumour necrosis factor α (TNFα), interleukin 1β (IL-1β), interleukin 6 (IL-6) and interleukin 8 (IL-8) have been most strongly associated with sepsis syndrome. In human and experimental animal models of sepsis, cytokines are released in a sequential manner resulting in a “cytokine cascade”. The cytokine cascade is initiated when a stimulus such as Gram-negative bacterial endotoxin induces production and secretion of early or “proximal” cytokines, which include TNFα and IL-1β. TNFα...
and IL-1β appear to mediate most of the physiological disturbances which are characteristic of sepsis. Infusion of either TNFα or IL-1β results in a sepsis-like state and specific blockers of either TNFα or IL-1β abrogate some of the manifestations of experimental sepsis. Proximal cytokines, as well as endotoxin, stimulate the production of later or "distal" cytokines, such as IL-6 and IL-8. Although the role of distal cytokines in sepsis is incompletely defined, they seem to intensify and perpetuate the inflammatory response and might have a role in tissue repair. IL-6 is a pleiotropic mediator whose actions include modulation of lymphocyte function, activation of coagulation and induction of hepatic acute phase protein synthesis. Interestingly, IL-6 may down-regulate TNFα and IL-1β production, which might be important in limiting the inflammatory reaction. IL-8 is a potent activator and chemoattractant for polymorphonuclear leucocytes and is thought to mediate neutrophilic tissue inflammation. It is possible that IL-8 mediates neutrophilic inflammation in the lungs and other organs and that this process leads to tissue damage and organ dysfunction.

Cytokines are not stored in intracellular compartments and are newly synthesized and released in response to inflammatory stimuli. This regulation occurs predominantly at the level of gene transcription with new expression of cytokine mRNA. Specific transcription regulating proteins (transcription factors) regulate cytokine gene transcription by binding to regulatory portions of cytokine genes, and activating or inhibiting transcription. Each cytokine has a variety of transcription factor binding domains in the promoter region of its gene which interact in complex ways to control cytokine gene transcription.

Much progress has been made in recent years in understanding the actions of individual transcription factors and unravelling the interactions of these factors in regulating transcription of specific genes. One transcription factor, nuclear factor κB (NF-κB), appears to play a central role in regulating the cytokine cascade. NF-κB is activated in many cell types by stimuli such as endotoxin, TNFα and IL-1β. NF-κB activation and promoter binding are crucial for transcription of many cytokines and related molecules, including TNFα, IL-1β, IL-6 and IL-8 [55]. Further characterizing the roles of NF-κB and other transcription factors will probably lead to better understanding of the process that initiates and regulates the cytokine cascade. Since NF-κB may be a pivotal point of regulation for the cytokine cascade, interventions to inhibit NF-κB activation could down-regulate systemic inflammation to a much greater extent than blocking the production or action of a single cytokine.

In addition to activating a pro-inflammatory cytokine cascade, inflammatory stimuli activate the production of specific cytokine neutralizing molecules and counter-inflammatory cytokines that can modify the host inflammatory response. Cytokine neutralizing molecules include soluble cytokine receptors and cytokine receptor antagonists. Cytokine receptors have an extracellular binding domain, a hydrophobic membrane anchoring domain and an intracellular signal transducing domain. Soluble cytokine receptors result from proteolytic cleavage of the extracellular binding domain which can be released into the circulation. Soluble cytokine receptors have been identified for both the p75 and p55 TNF receptor, the IL-1 receptor and the IL-6 receptor. Cytokine receptor antagonists are cytokine-like molecules that bind to cell surface receptors but do not initiate signal transduction. A receptor antagonist has been identified only for IL-1 (IL-1ra).

Paradoxically, soluble TNF receptor (sTNFR) and IL-1ra are released into the circulation in 10–100-fold excess compared with TNFα and IL-1β. Naturally released cytokine antagonists modulate the in vitro biological actions of the corresponding cytokines, but their function and importance in human sepsis are not well understood. In patients with sepsis syndrome, prognosis may be determined, at least in part, by the balance of cytokines and cytokine neutralizing molecules. In patients with non-lethal sepsis, both IL-1ra and soluble cytokine receptors may be shed into the circulation in sufficient concentrations to neutralize the quantities of cytokines produced. However, the concentrations of these inhibitors may be inadequate to prevent the deleterious effects of exaggerated pro-inflammatory cytokine release which occurs in lethal septic shock.

Cytokines have synergistic, overlapping and antagonist effects. Counter-inflammatory cytokines as well as pro-inflammatory cytokines are produced following activation of the cytokine cascade. One counter-inflammatory cytokine, interleukin 10 (IL-10), is released into the circulation in human sepsis and has been shown to block the production of TNFα, IL-1β and IL-8 in vitro. IL-10, like IL-6, might have a role in limiting the systemic inflammatory reaction by regulating pro-inflammatory cytokine gene expression. The clinical manifestations of sepsis syndrome are probably determined by a complex interaction between pro-inflammatory cytokines, counter-inflammatory cytokines and cytokine neutralizing molecules.

**Proximal cytokines**

**TUMOUR NECROSIS FACTOR α (TNFα)**

TNFα is a primary mediator of inflammation, and has been implicated in a large number of infectious and non-infectious inflammatory diseases [58]. TNFα is a 17-kDa protein produced primarily by mononuclear phagocytes, which has pleiotropic effects on target cells. Infusion of recombinant TNFα into humans results in SIRS with fever, haemodynamic abnormalities, leucopenia, elevated liver enzymes and coagulopathy [8, 51, 53, 64]. TNFα is capable of causing end-organ dysfunction which occurs in severe sepsis. In studies using chronically awake instrumented sheep, TNFα infusion caused pulmonary hypertension, hypoxaemia, decreased lung compliance and increases in pulmonary microvascular permeability [30, 71]. In human and animal models of sepsis induced by injection of bacterial endotoxin, TNFα production is quickly activated and can be detected in plasma.
Michie and colleagues infused *Escherichia coli* endotoxin into healthy volunteers and found that TNFα concentrations increased significantly and peaked 1 h after the infusion [39]. Several other studies have confirmed the observation that peak concentrations of TNFα are detected 60–90 min after endotoxin infusion [6, 28, 60].

TNFα appears to have a significant role in coordinating the inflammatory response and activating the cytokine cascade. *In vitro*, TNFα is a potent inducer of other cytokines, including IL-1β, IL-6 and IL-8. In baboons injected with *E. coli*, treatment with TNFα antibodies decreased the production of IL-1β, IL-6 and IL-8, in addition to reducing morbidity and mortality [17, 21, 29, 46, 63].

TNFα can be detected in the plasma of many patients with sepsis, and concentrations generally correlate with severity of illness and outcome. Endo and colleagues [18] showed that TNFα, IL-1β, IL-6 and interleukin 2 (IL-2) concentrations in plasma were higher in patients with septic shock compared with patients with sepsis alone or with other causes of shock. Waage and colleagues [70] reported that 10 of 11 patients who died of meningococcaemia had elevated serum TNFα concentrations, while only eight of 68 survivors had similar elevations. In contrast with these findings, some studies have failed to show that initial TNFα concentrations predict outcome. For example, Casey, Balk and Bone [7] reported that concentrations of TNFα, IL-1β, IL-6 and endotoxin in patients with sepsis were elevated compared with patients in an intensive care unit without sepsis, but TNFα concentration did not predict mortality independently. In this study, only 54% of patients with sepsis had detectable plasma TNFα concentrations.

Other studies have suggested that persistently elevated plasma TNFα concentrations portend a poor prognosis in patients with sepsis. Martin and colleagues [36] evaluated plasma concentrations of TNFα and IL-6 serially in 30 patients with septic shock. All patients had elevated plasma TNFα and IL-6 concentrations. Non-survivors had persistently higher TNFα concentrations than survivors, but no differences were noted in IL-6 concentrations. Pinsky and colleagues [43] reported that TNFα and IL-6 concentrations were higher in septic than non-septic shock, and that persistence of IL-6 and TNFα in serum rather than peak concentrations predicted a poor outcome in patients with shock.

Since TNFα can be induced rapidly by endotoxin, causes a septic-like state after infusion, can activate production of other mediators and is elevated in patients with clinical sepsis, it should be considered a central mediator of sepsis. Some of the disparity in clinical reports regarding the frequency of elevation of plasma TNFα in plasma of patients with sepsis and the ability of elevated plasma concentrations to predict outcome is related to the use of different assays (with different sensitivities) to detect TNFα concentrations. In addition, there is considerable variation in patient populations and timing of plasma TNFα measurements in these studies. Given these considerations, TNFα concentrations are usually elevated in patients with sepsis compared with other critically ill patients and these concentrations are higher in patients with septic shock; however, persistently elevated TNFα concentrations may be better predictors of outcome than single measurements.

**INTERLEUKIN 1 (IL-1)**

IL-1 is the term used for two related proteins, IL-1α and IL-1β. Both molecules activate the same IL-1 receptors and therefore share various biological activities. IL-1 is synthesized by mononuclear phagocytes, polymorphonuclear leukocytes and other cell types and affects a wide variety of tissues [16]. IL-1β is the predominant form of this mediator produced by endotoxin-stimulated human monocytes and detected in the plasma of septic animals. Both IL-1α and IL-1β mimic many of the biological activities of TNFα. Infusion of either form of IL-1 into humans causes fever, haemodynamic abnormalities, anorexia, malaise, arthralgia, headache and neutropenia [16, 56]. IL-1β is increased in humans after infusion of endotoxin, although at lower concentrations than TNFα [6, 28]. Like TNFα, IL-1β activates the production of other cytokines, including IL-6, IL-8 and TNFα. Further evidence of a primary role of IL-1β in sepsis syndrome is provided by studies using IL-1ra to block the biological activity of exogenous and endogenous IL-1β [15]. For example, prior treatment with IL-1ra decreased the mortality of rabbits treated with endotoxin [42]. In addition, Fischer and colleagues [20] reported that IL-1ra treatment reduced the production of IL-1, IL-6 and IL-8 (but not TNFα), and improved survival after *E. coli* infusion in baboons.

IL-1β is not normally present in human plasma, but has been detected in the plasma of patients with sepsis. McAllister and colleagues [38] reported cytokine measurements from three patients who developed sepsis after being transfused with packed erythrocytes contaminated with Gram-negative bacteria. These patients had detectable IL-1β that peaked by 4 h and subsequently returned to normal in the two survivors, but remained elevated in the non-surviving patient for 22 h. Plasma IL-1β can be detected in a minority of patients with sepsis but seems to be a measure of the severity of sepsis. Endo and colleagues [18] found that plasma IL-1β was elevated in only two of 40 patients with sepsis alone, but 15 of 22 patients with septic shock had elevated IL-1β concentrations. Casey, Balk and Bone [7] reported that 37% of patients with sepsis had initially detectable plasma concentrations of IL-1β, that the mean IL-1β concentration was higher in patients with sepsis than critically ill patients without sepsis and that the initial IL-1 plasma concentration did not predict mortality in patients with sepsis. A recent study by Goldie and colleagues [24] detected IL-1β in plasma of 29% of 146 patients with severe sepsis but no correlation with mortality was found. Taken together, the available studies of IL-1β in human sepsis show that IL-1β is elevated in plasma of some patients with sepsis. Initial plasma IL-1β
concentration may correlate with severity of sepsis, but no convincing independent association with mortality has been found.

**Distal cytokines**

**IL-6**

IL-6 is a 21-kDa glycoprotein produced by many cell types, including lymphocytes, fibroblasts and monocytes. IL-6 has a variety of biological effects, including activation of B- and T-lymphocytes, induction of acute phase protein production in the liver, and modulation of haematopoiesis [4]. In addition, IL-6 can activate the coagulation system [65] and function as a pyrogen [14]. In vitro, IL-6 suppresses the production of TNFα and IL-1β [1, 48]. The exact role of IL-6 in sepsis is uncertain. Infusion of IL-6 into experimental animals does not result in a sepsis-like state [44]. Xing and colleagues [72] transfected the IL-6 gene into rat lung tissue and found that expression of IL-6 resulted in lung lymphoid hyperplasia and acute phase protein production by the liver, without any other untoward effects.

Experimental injections of endotoxin or bacteria result in detectable plasma IL-6, with peak concentrations occurring subsequent to peak TNFα and IL-1 concentrations. After i.v. endotoxin injection into healthy human volunteers, Kuhns, Alvord and Gallin [32] found that plasma TNFα peaked at 1.5–2 h, whereas IL-6 peaked at 4 h. In baboons treated with sublethal doses of endotoxin or *E. coli*, plasma TNFα concentrations peak at 1–2 h, followed by IL-6 at approximately 3 h [11, 68]. In these same studies, lethal doses of *E. coli* caused peak plasma concentrations of TNFα at 2–3 h and peak IL-1β concentrations at 3–5 h, but IL-6 concentrations were still increasing 6–8 h after injection.

The appearance of plasma IL-6 in sepsis may be related directly to TNFα and IL-1 production. In mice, IL-1 and TNFα synergize to increase IL-6 production, and the production of IL-6 after endotoxin injection can be inhibited by prior treatment with anti-TNFα antibodies [52]. In addition, TNFα antibodies and IL-1ra attenuate IL-6 production in bacteraemic baboons [20, 21].

Although IL-6 is an integral part of the cytokine cascade, its individual role in the pathobiology of sepsis is unclear. In experimental animals, IL-6 blockade has not resulted in consistent benefit. Libert and colleagues [33] showed anti-IL-6 antibodies and antibodies to the IL-6 receptor offered some protection against lethal doses of TNFα in mice, but this protection could be overcome with higher doses of TNFα. In chimpanzees treated with endotoxin, monoclonal anti-IL-6 antibodies did not affect plasma TNFα concentrations, IL-8 concentrations, neutrophilic leucocytosis or neutrophil degranulation [65]. The major effect of anti-IL-6 antibody treatment in this study was to attenuate endotoxin-induced activation of coagulation.

IL-6 concentrations correlate more closely than other cytokines with severity and outcome of human sepsis, despite the fact that the role of IL-6 in this syndrome is not well defined. Plasma IL-6 may simply be a marker for activation of the cytokine cascade, and thus may reflect the association of host inflammatory response and disease severity. Hack and colleagues [26] reported that 32 of 37 patients admitted to an intensive care unit with sepsis had elevated IL-6 concentrations. IL-6 concentrations were higher in patients with septic shock, and IL-6 concentrations correlated with mortality. Damas and colleagues [12] reported serial measurements of TNFα and IL-6 in 40 patients with sepsis. In this study, peak serum IL-6 concentrations correlated with peak TNFα concentrations, APACHE II scores, and increased mortality. Several other studies [5, 7, 18, 24, 61] have confirmed this relation between IL-6 concentrations and the severity and outcome of sepsis. In addition, Moscovitz and colleagues [41] reported that in 100 patients admitted as emergencies and suspected of having bacteraemia, plasma IL-6 concentrations predicted bacteraemia and subsequent death from infection. IL-6 plasma concentration may also reflect severity of other diseases such as alcoholic hepatitis [54]. Based on the available information on IL-6 in human disease, plasma IL-6 concentration in sepsis appears to be a good indicator of activation of the cytokine cascade and predicts subsequent organ system dysfunction and death.

**IL-8**

IL-8 is a small, basic protein which belongs to the chemokine gene family of cytokines. IL-8 is produced by mononuclear phagocytes, polymorphonuclear leucocytes, endothelial cells, epithelial cells and a variety of mesothelial cell types in response to various stimuli, including endotoxin, IL-1 and TNFα. The primary function of IL-8 is to activate and chemotax within neutrophils to sites of inflammation. In addition, basophil and T-lymphocytes are attracted by nanomolar concentrations of IL-8, and IL-8 has been implicated an angiogenic factor [31].

When injected intradermally into humans, IL-8 induces a time-dependent perivascular neutrophil influx [62]. I.v. injection of IL-8 into baboons causes no haemodynamic abnormalities and no detectable production of TNFα, IL-1β or IL-6 [69]. Transient granulocytopenia followed by granulocytosis occurs, but no significant tissue neutrophil inflammation or injury. In human and primate models of sepsis, plasma IL-8 levels are detectable following endotoxaemia, and the kinetics mirror IL-6 plasma concentrations [32, 68]. In baboons, plasma IL-8 peaks after 2.5–3 h after a sublethal dose of endotoxin, whereas TNFα concentrations peak at 1 to 2 h [68]. Like IL-6, IL-8 production in sepsis appears to be activated by TNFα. Redl and colleagues [46] showed that treatment of baboons with anti-TNFα antibodies before *E. coli* infusion results in significantly decreased plasma IL-8 concentrations. In human sepsis, Marty and colleagues [37] and Hack and colleagues [27] have reported that plasma IL-8 concentrations are elevated in patients with sepsis and that higher concentrations correlate with mortality.
IL-8 may be important in mediating some of the organ dysfunction, including adult respiratory distress syndrome (ARDS), that occurs as a consequence of sepsis syndrome. IL-8 is present in bronchoalveolar lavage (BAL) fluid of patients with ARDS. BAL IL-8 concentration correlates with BAL neutrophil count and increased mortality in patients with ARDS [9, 40]. In a rabbit ischaemia-reperfusion lung injury model, where tissue injury is mediated at least partially by neutrophils (similar to ARDS), anti-IL-8 antibodies have been shown to have a protective effect [50]. Taken together, these data indicate that the function of IL-8 in sepsis is likely to be recruitment and activation of neutrophils in specific sites which can lead to tissue injury.

Soluble receptors and receptor antagonists

Soluble cytokine receptors

Soluble cytokine receptors have been described for TNFα, IL-1β and IL-6. Currently, the greatest amount of information regarding soluble cytokine receptors in sepsis syndrome examines the role of soluble TNFα receptors (sTNFR) [10]. Almost no data exist which define the role of the sIL-1R, sIL-6R or other soluble receptors in human sepsis syndrome. Soluble receptors have been described for both the p75 (sTNFR-p75) and p55 TNF (sTNFR-p55) receptor (also called the type I or type A and type II or type B TNFR, respectively). These soluble receptors are produced apparently by proteolytic cleavage of the extracellular binding domain of the TNF receptors from the cell surface. Since these sTNFR retain the ability to bind TNFα, they can modulate the actions of this cytokine. The proportion of free TNFα and TNFα bound to sTNFR exists in equilibrium and this balance may determine the bioactivity of a given TNFα concentration.

Plasma sTNFR concentrations are present in normal humans and are released in excessive amounts into the circulation in response to endotoxaemia. In healthy human volunteers, endotoxin injection results in a 4–5-fold increase in sTNFR concentration by 3 h, with peak plasma concentrations 10 times that of TNFα [57]. Van Zee and colleagues [67] showed that the kinetics of TNFα production and sTNFR shedding are different in experimental models of sepsis. In these experiments, plasma TNFα concentration peaked 1 h after endotoxin injection, but plasma sTNFR concentration peaked at 3 h. In human sepsis, sTNFR is increased and correlates with severity of illness and mortality. Ertel and colleagues [19] reported that plasma concentrations of both species of sTNFR were increased in patients with sepsis and correlated with APACHE II score, multiple organ failure score and mortality. These findings were supported by Goldie and colleagues [24] who found that higher plasma sTNFR concentrations predicted mortality in a group of patients with severe sepsis.

The role of sTNFR in sepsis is incompletely understood, as is the relation between elevated plasma sTNFR and increased mortality. Plasma sTNFR concentrations may simply be a marker for the exaggerated inflammatory state and not reflective of TNFα/sTNFR ratios in certain tissues or at critical times. Alternatively, the TNFα-sTNFR complex may serve as a slow release reservoir of TNFα, which could perpetuate the inflammatory response.

IL-1 receptor antagonist (IL-1ra)

IL-1ra was first identified as a 23 kDa protein purified from the urine of patients with monocytic leukaemia [49]. The amino acid sequence for this protein is 26 % homologous to IL-1β and 19 % homologous to IL-1α. IL-1ra blocks IL-1 activity by competing for binding to type 1 and type 2 IL-1 receptors without causing signal transduction [16]. IL-1ra can attenuate endotoxin effects in animal models of sepsis [20, 42]. In human volunteers, plasma IL-1ra concentrations are increased after endotoxin injection, with peak concentrations at 3–4 h [32]. In humans with sepsis, IL-1ra is present in plasma at markedly higher concentrations than IL-1, but its function in this setting is uncertain. Gardlund and colleagues [22] reported that 11 of 13 patients with septic shock had plasma IL-1ra/IL-1β ratios >2000. van Deuren and colleagues [66] found significantly higher plasma IL-1ra concentrations in patients with meningococcaemia and shock than in patients with meningococcal meningitis alone. Goldie and colleagues [24] reported that plasma IL-1ra concentrations were elevated in patients with severe sepsis, but concentrations did not correlate with outcome in this group of patients.

Counter-inflammatory cytokines

IL-10

In addition to pro-inflammatory cytokines, cytokines with predominantly counter-inflammatory actions have been identified. IL-10 was first described as a product of TH2 lymphocytes that inhibits cytokine production by activated macrophages. In vitro, IL-10 can inhibit production of TNFα, IL-1, IL-6 and IL-8 [35]. Gerard and colleagues [23] showed that treatment of mice with IL-10 before endotoxin could prevent endotoxin-induced mortality and diminish plasma TNFα release. Additionally, Rogy and colleagues [47] demonstrated that transfucting mice with the human IL-10 gene resulted in transgene expression in the animals, and that these animals were protected from lethal doses of endotoxin. Finally, treatment of mice with anti-IL-10 antibodies has been shown to increase endotoxin-induced TNFα release and worsen mortality [35].

Recent human studies have shown that IL-10 is detectable in plasma of patients with sepsis [13, 25, 34, 66], van Deuren and colleagues [66] found significantly higher plasma IL-10 concentrations in patients with septic shock compared with patients without shock. This finding was corroborated by Marchant and colleagues [34], who reported that higher IL-10 concentrations were present in patients with septic shock than in patients with sepsis alone. The importance of IL-10 in human sepsis is currently uncertain.
Anticytokine treatment strategies

With increasing evidence that activation of the cytokine cascade is of critical importance in determining the pathobiology of sepsis, there has been increasing enthusiasm for treatments to interrupt this cascade. Current human trials utilizing anticytokine treatments for sepsis have been reviewed recently by Suffredini [59]. Three anticytokine treatment strategies have been evaluated in humans with sepsis: (1) blocking endotoxin effects with polyclonal or monoclonal endotoxin antibodies, (2) blocking TNFα effects with anti-TNFα antibodies or with TNF receptor constructs, and (3) blocking the actions of IL-1 with IL-1ra.

To date, human trials of anticytokine therapy have been relatively disappointing with regard to identifying treatments to improve survival in sepsis. The reason for this lack of efficacy is unclear. Certainly, the timing and dose of these interventions may be critical, since these treatments affect proximal steps in the cytokine cascade. Once the cascade is activated, interventions to decrease proximal cytokine actions may be insufficient to improve outcome significantly. In addition, cytokines have redundant and overlapping functions so that blocking the production or action of single cytokines may not affect outcome. Finally, blocking cytokine production may inhibit host defense functions that are critical for recovery from sepsis. There may be a balance between excessive inflammation which causes tissue injury and inadequate inflammatory response which compromises host defence functions.

Therapies designed to modulate activation of the cytokine cascade are certainly attractive and may eventually prove beneficial in sepsis. A better approach than current treatment strategies may be to modulate the cytokine cascade by targeting elements that control production of both proximal and distal cytokines, such as the transcription factor NK-xB. Counter-inflammatory molecules such as IL-10 may also be capable of globally modifying the cytokine cascade. Regardless of the therapeutic approach, future studies for the treatment of sepsis should be conducted as prospective, randomized placebo-controlled, multi-centre clinical trials [3]. These trials will require close cooperation between basic scientists, clinicians and pharmaceutical companies.

Summary

Sepsis is a constellation of clinical signs and symptoms resulting from excessive systemic host inflammatory response to infection. This inflammatory response is largely mediated by cytokines, which are released into the systemic circulation. Plasma concentrations of specific cytokines, TNFα, IL-1β, IL-6 and IL-8 are frequently elevated in human sepsis and cytokine concentrations correlate with severity and outcome of sepsis. In addition to pro-inflammatory cytokines, soluble cytokine receptors, cytokine receptor antagonists and counter-inflammatory cytokines are also produced in large quantities in patients with sepsis; however, the specific role of these molecules in sepsis remains undefined. A complex interaction of cytokines and cytokine-neutralizing molecules probably determines the clinical presentation and course of sepsis. Intervening in this sequence of events to modify the host inflammatory responses may prove to be a beneficial treatment strategy for sepsis, but currently tested anticytokine therapies have been largely unsuccessful.

References


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