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Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: What we do and do not know about cytokine regulation

[Special Article]

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Outline

Graphics

Abstract

Objectives: The systemic inflammatory response syndrome (SIRS) is the massive inflammatory reaction resulting from systemic mediator release that may lead to multiple organ dysfunction. The objective of this review article is to analyze the roles of cytokines, cytokine production, and the relationship of cytokine production to the development of SIRS.

Data Sources: Previous research and clinical studies related to cytokines and their relationship to SIRS.

Study Selection: From the studies reviewed, three critical questions are addressed. First, what is the definition of increased cytokine concentrations? Second, what other systemic illnesses besides sepsis can alter cytokine concentrations? Third, what are the right cytokines to measure?

Data Synthesis: This article postulates a three-stage development of SIRS, in which stage 1 is a local production of cytokines in response to an injury or infection. Stage 2 is the protective release of a small amount of cytokines into the body's circulation. Stage 3 is the massive systemic reaction where cytokines turn destructive by compromising the integrity of the capillary walls and flooding end organs.

Conclusions: While cytokines are generally viewed as a destructive development in the patient that generally leads to multiple organ dysfunction, cytokines also protect the body when localized. It will be necessary to study the positive effects of cytokines while also studying their role in causing SIRS. It will also be important to investigate the relationship between cytokines and their blockers in SIRS.

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Virtually all patients with sepsis experience dysfunction of at least one organ; multiple organ dysfunction occurs in approximate 30% of such patients [1]. Multiple organ dysfunction can also be found in more than equals 30% of trauma patients [2], 24% of patients with acute pancreatitis [3], and in roughly one third of burn victims [4,5]. How the dysfunction of multiple organs can be produced by such disparate disorders has long troubled physicians. Almost 10 yrs ago, it was suggested that multiple organ dysfunction might result not from infection per se, but from a generalized inflammatory reaction [6]. Only recently, however, has evidence accumulated to support that hypothesis [7].

This evidence suggests that a massive inflammatory reaction resulting from systemic

cytokine release is the common pathway underlying multiple organ dysfunction. The clinical sequelae of this inflammatory reaction has been termed the "systemic inflammatory response syndrome" (SIRS).

Unfortunately, the more we learn about this inflammatory response, the more difficult it becomes to pinpoint a specific cytokine, or a specific reaction, as the "cause" of SIRS. To some extent, cytokine release is a normal, healthy part of the body's response to insult or infection. Cytokines are highly pleiotropic, and they appear capable of producing markedly different effects depending on the nearby hormonal milieu. Furthermore, the body has a highly complex, tightly regulated network of receptor antagonists and other regulatory agents that continuously modulate the effects of cytokine release. (This fact may explain why the trials of various anticytokine agents have produced disappointing results to date.)

Adding further to our confusion is the fact that systemic cytokine release can occur in a variety of disorders without leading to organ dysfunction Table 1. Even in those disorders that are often associated with organ dysfunction, the pattern of systemic cytokine release is dissimilar. How, then, can we explain SIRS and multiple organ dysfunction?

Acquired immunodeficiency syndrome
Advanced age
Alcohol
Alcoholic hepatitis
Alcoholic liver cirrhosis
Asthma
Atherosclerosis
Autoimmune thyroiditis
Bowel necrosis
Cardiac myxoma
Cardiopulmonary resuscitation
Castleman's disease
Coal workers' pneumoconiosis
Congestive heart failure
Diabetes (insulin-dependent)
Graft-vs.-host disease
Hemodialysis
Hypernephromas
Inflammatory bowel disease
Ischemia-reperfusion injury
Kaposi's sarcoma
Multiple myeloma
Myeloblastic leukemia (acute)
Myelogenous leukemia (acute and chronic)
Myocardial infarction (acute)
Mycosis fungoides
Non-A, non-B hepatitis (chronic)
Osteomyelitis
Ovulation
Malaria
Multiple sclerosis
Osteoporosis
Parasitic infections
Periodontal disease
Premature labor secondary to uterine infection
Primary biliary cirrhosis
Psoriasis
Rheumatoid arthritis
Strenuous exercise
Systemic lupus erythematosus
Transplant rejection
Unstable angina

Table 1. Conditions that have been associated with increased cytokine levels

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PATTERNS OF CYTOKINE RELEASE

Cytokine release during sepsis has been extensively reviewed by myself and others [8-12], and thus will not be detailed here. Instead, this discussion focuses on the patterns of cytokine release in burn patients, trauma and hemorrhage victims, and patients with pancreatitis. I

focus on release of what appear to be three of the most important cytokines: tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6. Although these cytokines are not the only ones to play a role in the onset of SIRS, a complete discussion of all cytokines is beyond the scope of this article.

For comparative purposes, note that in sepsis, TNF appears to be the first cytokine to be released systemically, followed shortly thereafter by IL-1, then IL-6 [2]. In patients with severe sepsis, peak serum TNF concentrations occur within 2 hrs after the onset of sepsis. In contrast, peak IL-6 concentrations occur within 4 hrs after the onset of sepsis [13].

BURN INJURY

Tumor Necrosis Factor.

What role TNF plays in the inflammatory response to burn injury is presently unclear. Bone marrow macrophages from burned guinea pigs produce significantly more TNF than do similar macrophages from healthy animals [14]. However, studies in human burn victims have produced conflicting results.

Guo et al. [15] failed to detect increased TNF concentrations in patients with burn injury at any time during 3 wks' follow-up. In contrast, Cannon et al. [16] found that TNF concentrations were increased initially in patients with second- or third-degree burns, and fluctuated thereafter. Marano et al. [17] also found that TNF concentrations fluctuate for at least 4 wks after severe burn injury.

One explanation for these discordant results may be the very fact that TNF concentrations fluctuate (reasons for this fluctuation are discussed in more detail below). Measurements obtained periodically (as occurs in most studies) may not reflect a patient's ongoing course. Another possible explanation is that increased TNF concentrations are a marker of infectious complications in burn patients. In the study by Marano et al. [17], circulating TNF concentrations were more likely to be detectable in patients with burn injury and sepsis than in those patients with burn injuries but not sepsis.

In the study by Marano et al. [17], increased TNF concentrations were associated with an increased risk of death. In contrast, TNF concentrations correlated poorly with outcome in the study by Cannon et al [16].

Interleukin-1.

Evidence from animal studies [14,18,19] suggests that in the absence of infectious complications, increased circulating IL-1 concentrations are uncommon after burn injury. However, local production of IL-1 may be high [20,21].

In human trials, evidence suggests that circulating IL-1 concentrations increase initially after second- or third-degree burn injury and fluctuate thereafter [16]. However, the extent of the IL-1 response correlates inversely with burn size. Furthermore, low circulating IL-1 concentrations are associated with an increased risk of death. As a result of these findings, Cannon et al. [16] suggested that IL-1 is an essential mediator of host defenses.

Experimental data support this hypothesis. For example, in mice given a 15% burn injury followed by burn wound inoculation of Pseudomonas aeruginosa, injection of IL-1 improved survival and lowered the frequency of subsequent bacteremia [22]. The administration of IL-1 and indomethacin has also been shown to improve survival rates in mice given cecal ligation and puncture after burn injury [19]. The combination treatment also attenuates the increase in TNF and IL-6 concentrations that normally follows this septic/thermal challenge. Mills et al.

[18] postulated that a lack of circulating IL-1 response may represent a "window of immunodeficiency" after burn injury.

Interleukin-6.

A number of human studies [15,23-26] have shown that IL-6 concentrations increase rapidly after severe burn injury. Concentrations may reach ten to 100 times above normal within a few hours after the initial injury, and these concentrations may remain increased for several weeks or longer [25]. Markedly increased IL-6 concentrations predict a poor prognosis [15,23,24].

In most studies, the extent of the increase in IL-6 concentrations correlates directly with the extent of burn injury [23,24]. The extent of burn injury may also influence how long IL-6 concentrations remain increased [15]. However, although IL-6 concentrations remain increased, they fluctuate over time [26]. Furthermore, there is wide interindividual variability in the extent of the IL-6 response [15]. Whether infection contributes to this variability remains unclear; evidence is conflicting [15,23].

The complexity of the circulating IL-6 response to severe burn injury is perhaps best demonstrated in a study by Schluter et al [23]. The presence of sepsis was confirmed in seven of 21 patients in this study, all of whom died. The other 14 patients survived; five of these surviving patients had suspected (but not confirmed) sepsis. In the nine patients who never developed sepsis and the five patients with suspected sepsis, IL-6 production was maximal in the first three postburn days. IL-6 production then gradually returned to normal by 30 to 50 days after burn. In the seven nonsurvivors, IL-6 production was even higher during the first 3 days, but it then continued to increase until death (usually between days 10 and 19).

In this study [23], IL-6 concentrations in survivors with suspected sepsis continued to decrease, even when clinical symptoms of sepsis became manifest. In nonsurvivors, however, the greatest increase in IL-6 concentrations occurred just before, or during, the onset of clinical sepsis. Schluter et al. [23] hypothesized that both thermal injury and sepsis prompt systemic IL-6 release, but they do so in different degrees and at different times after burn injury.

Changes in IL-6 concentrations have also been associated with changes in the proportions of circulating T and B cells [15,27], with alterations in circulating platelet concentrations [25], and other evidence of bone marrow stimulation. Bone marrow stimulation, coupled with changes in the types of cells produced, may represent one of the fundamental steps in the development of SIRS.

TRAUMA/HEMORRHAGE

Both cellular and humoral immunity may be decreased in patients with severe injury, leaving patients at risk for sepsis [28-31]. One marker of this decreased immunity may be anergy to skin test reactions. For example, in a study by Browder et al. [32], anergy persisted for at least 1 wk in 15 of 38 trauma patients. Eight of 15 anergic patients developed sepsis. In contrast, only two of 23 patients who were reactive on day 7 developed sepsis. Other researchers [33] have found that anergy to hypersensitivity skin tests identifies postoperative patients at high risk for sepsis.

It is not clear what causes this anergy. Trauma and hemorrhage induce release of a number of agents that alter immunologic function, including prostaglandins, catecholamines, and corticosteroids [34]. However, there is evidence that changes in cytokine concentrations may accompany, and perhaps produce, this anergic response.

Tumor Necrosis Factor.

Whether trauma per se increases circulating TNF concentrations is unclear. A number of studies [2,35-37] suggested that in the absence of clinically important blood loss, posttraumatic circulating TNF concentrations are normal or only minimally increased. However, when blood loss is substantial, circulating TNF concentrations can increase markedly [38,39].

Ayala et al. [40] demonstrated that increased circulating TNF concentrations occur 4 hrs after trauma and maximal hemorrhage. When hemorrhage is unaccompanied by trauma, peak TNF concentrations occur 2 hrs after maximal hemorrhage. However, peak TNF concentrations are much lower than those concentrations measured after trauma/hemorrhage [41]. The increased circulating TNF concentrations persist for at least 4 hrs after volume resuscitation [39].

Interleukin-1.

Within the first few hours after traumatic injury, circulating IL-1 concentrations are undetectable [2,37,42]. There is evidence that IL-1 production is depressed for at least 5 days after traumatic injury [43]. (IL-2 production may also be decreased after trauma [44].)

The lack of IL-1 production seems surprising, given that patients with multiple traumatic injuries have a marked increase in monocyte concentrations [45]. A partial explanation may come from the studies of Faist et al. [45], who showed that monocytes taken from patients undergoing elective surgery have a severe impairment of lipopolysaccharide-stimulated IL-1 and IL-8 synthesis. (IL-6 synthesis occurs after lipopolysaccharide stimulation, but its onset is delayed.) These authors [45] speculated that soon after traumatic insult, several priming factors affect monocytes: emergency recruitment, functional immaturity, and circulating suppressor factors. As a result, there is an overwhelming monocytosis, but the cell population is characterized by fundamental functional disorders.

The lack of an IL-1 response may contribute to the anergy that often occurs in trauma patients. An increase in circulating IL-1 concentrations precedes the conversion of a negative to positive skin test in these patients [32].

Interleukin-6.

Circulating IL-6 concentrations are increased after elective surgery or tissue injury [35-37]--even in the absence of clinically important blood loss [35,40]. However, IL-6 release increases markedly if trauma is accompanied by hemorrhage [35]. Peak IL-6 concentrations correlate with the volume of blood lost [46].

The increase in circulating IL-6 concentrations occurs within 1 to 2 hrs after traumatic injury [2,37]. How long IL-6 concentrations remain increased is unclear. Increased concentrations have been reported to remain increased for at least 1 to 3 days after traumatic injury [2,37]. However, in at least one study [44], posttraumatic circulating IL-6 concentrations remained increased for up to 21 days.

Ayala et al. [41] showed in an animal study that even relatively minor insults, such as skin incision and catheter insertion, are sufficient to induce IL-6 release. This finding holds true even when these procedures are carried out under aseptic conditions [41]. (Whether anesthesia administration influences IL-6 production is unclear; the evidence is conflicting [47,48].) When rats are subjected to laparotomy and hemorrhage, IL-6 concentrations peak at the point of maximal hemorrhage. TNF concentrations peak 4 hrs later [40]. The increased IL-6 concentrations persist even after the animals are resuscitated [39].

IL-6 concentrations may increase even further when sepsis complicates traumatic injuries. In patients with multiple traumatic injuries, extremely high IL-6 concentrations correlate with the development of infectious complications [44].

Where does the excess IL-6 come from? T-cell cultures obtained from patients with multiple traumatic injuries produced markedly increased amounts of IL-6 [44]. However, these patients showed no evidence of altered T-cell proliferation. Most of the IL-6 appeared to come from monocytes--specifically, an Fc receptor-positive monocyte subset (Fc gamma RI^{plus}) [49-51]. Patients who become immunosuppressed during their postinjury course have an increased proportion of this Fc gamma RI^{plus} monocyte subset [49], which may explain why monocytes from these patients produce higher IL-6 concentrations than do monocytes from controls or immunocompetent trauma patients. Support for an association between increased IL-6 concentrations and posttraumatic immunosuppression comes from animal work [39], which shows that increased IL-6 concentrations correlate with alterations in hepatocellular function.

PANCREATITIS

Tumor Necrosis Factor.

TNF may be one of the chief mediators of inflammation in acute pancreatitis [52]. Guice et al. [52] demonstrated that TNF concentrations increase during the course of cerulein-induced pancreatitis, and that the extent of the increase correlates with the extent of edema formation in the pancreas and lungs. Campbell et al. [53] showed that the administration of TNF and interferon-gamma induces piloerection, abdominal swelling due to ascites, thymic atrophy, splenic enlargement, and edematous enlargement of the pancreas. Histologic examination has demonstrated a generalized infiltration of lymphocytes and polymorphonuclear cells in the pancreas, areas of hemorrhagic necrosis, ductal dilation, and intralobular and subcapsular edema [53]. High circulating TNF concentrations have also been found in a study by Exley et al. [54] of patients with severe pancreatitis.

Whether the increased TNF concentrations are always harmful remains unclear, however. In animals, pretreatment with an anti-TNF antibody increases pancreatic edema formation after cerulein injury [52]. In patients with pancreatitis, decreased concentrations of TNF (or IL-6) appear to be a harbinger of death [55]. Hamilton et al. [55] suggested that these low cytokine concentrations signal an anergic immune status and that the inability to mount an appropriate cytokine response portends a poor prognosis.

Interleukin-1.

A MEDLINE search from 1980 to 1994 using the terms "IL-1" and "pancreatitis" failed to reveal any studies addressing IL-1 concentrations in patients with pancreatitis.

Interleukin-6.

Studies [56-58] have shown that circulating IL-6 concentrations increase early in the course of acute pancreatitis and correspond with disease severity. For example, Leser et al. [56] followed the course of 50 patients with acute pancreatitis. In the 25 patients with mild disease, IL-6 concentrations were slightly increased initially and returned toward normal within 4 days. In 15 patients who survived severe pancreatitis, initial IL-6 concentrations were markedly increased. These concentrations decreased thereafter but remained slightly increased by day 7. The ten patients who died of severe pancreatitis had extremely high initial IL-6 concentrations. Although these concentrations had decreased somewhat by day 7, they remained high.

Circulating IL-6 concentrations may also predict prognosis in acute pancreatitis. In the study by Leser et al. [56], high initial IL-6 concentrations predicted a severe or lethal outcome. Heath et al. [58] found that increased peak IL-6 concentrations can distinguish between severe and mild attacks of pancreatitis.

Peak IL-6 concentrations follow the onset of symptoms of pancreatitis by 24 to 36 hrs [58]. C-reactive protein concentrations appear to follow the course of IL-6 concentrations, with a delay of 1 day [56]. IL-6 may be the principle mediator of the acute-phase response [58].

PROBLEMS ASSOCIATED WITH THESE STUDIES

Before we can understand how these studies illustrate the development of SIRS, several problems associated with the studies must be addressed.

What Is an "Increased" Cytokine Concentration?

When cytokines were first discovered, it was generally assumed that their presence in the circulation signaled pathology. It is still often stated that cytokines cannot be detected in serum from normal persons. Strictly speaking, that may be true, although several studies [59-62] have documented low serum cytokine concentrations in healthy volunteers. However, a problem is presented by the term "normal person." If we look at the list of conditions that can alter circulating cytokine concentrations, it is clear that a "normal person" must be a young adult with no acute or chronic diseases who does not drink excessively, does not exercise strenuously, and has not ovulated recently. But how many of our patients with sepsis or other forms of SIRS can meet these criteria?

In other words, how many patients who were included in studies of sepsis, burn injury, trauma, or pancreatitis had preexisting conditions that might at least partially explain the measured cytokine concentrations? The number is often surprisingly high. Patients with sepsis tend to be older, and often have cancer, diabetes, or other underlying chronic diseases. Patients with pancreatitis may have underlying alcoholic liver disease. (Alcohol alone seems to be able to alter cytokine production [63,64]; it is not necessary for liver dysfunction to develop.)

Trauma studies are often conducted in patients who have undergone elective cardiovascular, oncologic, or orthopedic surgery (often, for disorders that cause increased cytokine concentrations). For example, in one study [36] that reported increased IL-6 concentrations in 13 patients undergoing elective surgery, two of the patients had undergone cardiopulmonary by-pass and five patients suffered from bowel cancer. Eight of the patients were elderly.

This fact is not to say that sepsis or other forms of SIRS do not increase cytokine concentrations directly. These disorders usually produce cytokine concentrations that are markedly higher than those concentrations resulting from chronic disease. However, we currently lack a clear understanding of where the cutoff points are between "normal," "chronic low increase," and "acute high increase" values.

Another developing body of knowledge is the presence and relationship of anti-inflammatory cytokines and other endogenous antagonists (anti-endotoxin core antibodies, IL-1-receptor antagonists, and soluble TNF receptors) to the proinflammatory cytokines.

What Other Factors Can Alter Cytokine Concentrations?

There is considerable interindividual variation in cytokine production. As noted, some healthy persons may have high cytokine concentrations, without untoward effects. This phenomenon may be related to the molar relationship to endogenous antagonists in these individuals. In contrast, some patients with severe sepsis, extensive burns, or multiple trauma may never have detectable cytokine concentrations. In addition to preexisting disease, several other factors may help explain these variations.

For example, there is evidence that a person's HLA haplotype influences the body's ability to produce cytokines, particularly TNF [65]. Both age and gender have also been shown to influence cytokine release [43]; estrogen seems to have a particularly potent effect [66].

The complexity of the etiology of SIRS with multiple organ dysfunction has prompted the hypothesis of a reaction to a second insult that produces a different response to the first Figure 1. The first insult could be trauma, burns, and surgery, with sepsis being the second insult. In each reaction, the second insult has an altered response to an injury that is primed by the first. This altered response is probably due to the initial activation by the first insult, which can also be altered by, or delayed by, inadequate resuscitation. The sequence could also be reversed [67,68].

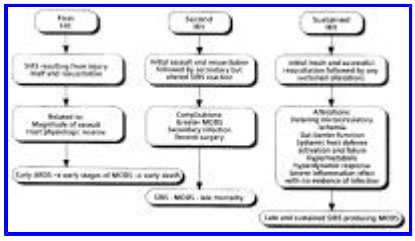

Figure 1. First hit, second hit, and sustained hit that can occur with systemic inflammatory response syndrome (SIRS). ARDS, adult respiratory distress syndrome; MODS, multiple organ dysfunction syndrome.

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Some animal studies also demonstrated problems with other illnesses caused by sepsis. For example, in a rat study by Minei et al. [69], thermal injury induced priming of alveolar macrophages and an increase in macrophage TNF production, which was further complicated by a future exposure to lipopolysaccharide. Acid aspiration caused systemic findings that are identified as SIRS [70]. In a study by Ayala et al. [71] in mice, hemorrhage followed by resuscitation was accompanied by an eicosanoid-induced, IL-4 and IL-10, cell-mediated state of immunosuppression. Similarly, a rabbit study by Mileski et al. [72] showed that hemorrhagic shock followed by resuscitation ended in a proinflammatory state, resulting in greater sensitivity to the negative effect of lipopolysaccharide infusion.

In other examples of complications that occur after sepsis, an initial assault and successful resuscitation may be followed by sustained physiologic alterations. These alterations include microcirculatory ischemia, deteriorating gut barrier function, systemic host defense activation and failure, hypermetabolic, hyperdynamic response, or severe inflammation, often with no evidence of infection. Such sustained alterations ultimately lead to late and sustained SIRS, producing multiple organ dysfunction syndrome and death [68].

There is the possibility that sepsis tissue injury is a result of programmed cell death, known as apoptosis. Apoptosis usually limits the cell population, with rapid proliferation of the gut epithelium. Exposure to inflammatory mediators, such as lipopolysaccharide, cytokines, and reactive oxygen species, causes parenchymal and endothelial cells to respond by the induction of stress gene expression. These cells, after exposure to these mediators, then undergo an increase in apoptosis [73].

Cytokine release also appears to have circadian periodicity [74,75]. Although these

fluctuations are fairly small, they could influence the results of studies in which cytokine concentrations are assayed infrequently (i.e., twice daily or less).

Are We Measuring the Right Cytokines?

This question is perhaps the most important one of all. Virtually all studies of patients with sepsis, burn injury, trauma, or pancreatitis have assayed circulating cytokine concentrations. However, most cytokines, if not all, have two forms: a) the circulating form; and b) a cell-associated form [76]. For example, TNF exists as a 17-kilodalton secreted form and a 29-kilodalton cell-associated form [77]. IL-1 also exists in two forms: a) a cell-associated form (IL-1 alpha), which usually remains within cellular cytosol, although it may migrate to the cell membrane; and b) a systemic form (IL-1 beta), which can be produced in large quantities and released into the circulation and the extracellular space [78].

The relationship between cell-associated cytokines and their circulating counterparts is presently unclear. The cell-associated forms might be precursors of the systemic cytokines, but this possibility has not been demonstrated. As expected, cell-associated cytokines are produced at local areas of injury. This local production seems to precede systemic cytokine release. For example, blister fluid obtained from patients 12 to 16 hrs after burn injury contained substantial amounts of IL-1 alpha; IL-1 beta was not detected [21]. The source of the IL-1 alpha appears to be the injured keratinocyte [21].

Unfortunately, very little is known about how local production of cell-associated cytokines eventually leads to local production of circulating cytokines. Even less is known about how local production of circulating cytokines can eventually result in systemic production. In one study [42] of mice given skin incisions, IL-1, IL-6, and TNF were all found in the wound fluid. In contrast, IL-1 was never detectable in serum, and circulating IL-6 concentrations were markedly below wound fluid concentrations [42]. (Serum TNF concentrations were not reported.)

In another study [79], guinea pigs were given intratracheal injections of Escherichia coli. Two hours after the injection, TNF was detectable in the bronchoalveolar lavage fluid of 95% of the animals and in the serum of 75% of the animals. Eight hours after the injection, TNF concentrations in both bronchoalveolar lavage fluid and serum had decreased considerably. Two observations in this study were particularly interesting. First, TNF concentrations in bronchoalveolar lavage fluid correlated with, but were markedly higher than, serum concentrations. Second, TNF was detectable in serum only when bronchoalveolar lavage fluid concentrations were more than 400 units/mL. It is therefore tempting to speculate that when a critical concentration of local cytokine production is reached, systemic spillover occurs. This situation may well be the case, but it may not be the only way in which circulating cytokines are produced. Experimental evidence suggests that the ability of monocytes to produce cell-associated cytokines does not correlate with circulating cytokine concentrations [76]. Thus, other mechanisms for systemic cytokine production must come into play.

Assays of circulating cytokine concentrations may be misleading because they do not detect cytokines bound to soluble receptors. These assays may also fail to detect cytokines when inhibitors or receptor antagonists are present [78]. Direct measurements of endogenous antagonists (antiendotoxin core antibodies, IL-1-receptor antagonists, and soluble TNF receptors) are now possible. Studies on the relationship between endogenous antagonists and proinflammatory cytokines in patients are needed. Nevertheless, it is possible that by focusing on circulating cytokine concentrations, we have overlooked a more important issue: How and why are cytokines produced locally, and what effect do they have on local tissues? Deitch [80] suggested that cytokines act predominantly as paracrine and autocrine

messengers, not endocrine mediators. Thus, cytokines may exert their major effects locally, within organs and tissues [80].

TOWARD A THEORY REGARDING THE PATHOGENESIS OF THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

I propose that there are three stages in the development of SIRS Figure 2.

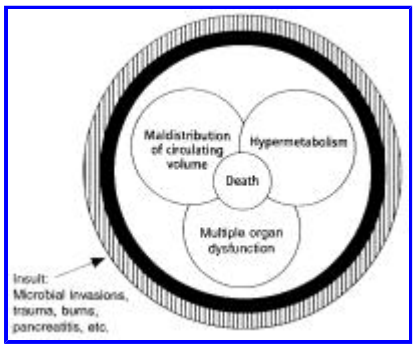

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Figure 2. Three stages of the systemic inflammatory response syndrome reaction.

Stage 1.

In response to injury or infection, the local environment produces cytokines. Among their other effects, these cytokines help promote wound repair and they recruit cells to combat pathogenic organisms. However, very little is currently known about the effects of cytokines in the local milieu.

Stage 2.

Small amounts of cytokines are released into the circulation. (This amount may be so small as to often be undetectable.) Again, this cytokine release is directed toward defense of the local environment. Macrophages and platelets are recruited; production of growth factors is stimulated. An acutephase response may be initiated. At this stage, the cytokine response cannot be thought of as pathologic or abnormal. Rather, the cytokine response represents part of the body's main line of defense. The acute-phase reaction is controlled by a diminution of the proinflammatory mediators and a simultaneous increase in endogenous antagonists, such as the IL-1-receptor antagonists.

Under normal circumstances, this cytokine response is tightly regulated by an intricate network of mediators, including other cytokines, receptor antagonists, and antibodies. These mediators keep the initial inflammatory response in check both by down-regulating cytokine production and by counteracting the effects of cytokines already released. The wound is healed, the infection is fought off, and homeostasis is restored.

Occasionally, the body finds it impossible to reestablish homeostasis, and stage 3 (SIRS) sets in. However, given the wide variety of disorders that can prompt systemic cytokine release, and the complexity of the cytokine response to injury and infection, what is surprising is not how frequently control is lost but how often it is maintained.

Stage 3.

When homeostasis cannot be restored, a massive systemic reaction begins. It is only at this stage that the predominant effects of cytokines become destructive rather than protective. As

the circulation becomes flooded with inflammatory mediators, the integrity of the capillary walls is destroyed. Cytokines spill out into end organs, producing additional sites of damage. Unless the inflammatory reaction can be brought back under control, multiple organ dysfunction and death may ensue.

WHY IS CONTROL LOST?

If we accept this paradigm for how SIRS develops, then we must ask another question: Why is control of the initial cytokine response lost? Evidence suggests that this loss of control can happen in a number of ways, reflecting alterations in both cytokine production, metabolism, and concentrations of endogenous antagonists. As the evidence presented above indicates, the pathway leading to SIRS may be different, depending on whether the initial insult was sepsis, trauma, massive burns, or pancreatitis. Even within these categories of injury, however, there may be interindividual variations in how SIRS can develop.

Inappropriately High or Low Cytokine Production.

Perhaps the most obvious way in which SIRS can develop is in patients who produce excessive quantities of one or more cytokines. For example, release of both TNF and IL-6 is increased in patients with liver cirrhosis [81]. When such patients become infected, cytokine production increases even further. Patients with cirrhosis and septicemia have TNF-alpha and IL-6 concentrations that are markedly higher than those concentrations found in patients with cirrhosis and no infection, or in patients with septicemia but no cirrhosis [81]. This finding suggests that monocytes from patients with alcoholic cirrhosis are preactivated to secrete excessive cytokine concentrations in response to an additional stimulus, such as infection.

Other studies [50,51] have found that monocytes can respond differently to the same stimuli, depending on their previous state of activation. For example, IL-6 normally prompts release of TNF and IL-1. However, in some settings, IL-6 can inhibit release of these other cytokines [82,83]. This finding may help explain why some patients fail to mount an appropriate cytokine response to infection or injury [16,18]. Given the intricate network that regulates the effects of cytokines, the absence of a particular cytokine may be as dangerous as the increased production of another cytokine. The intricate relationship between cytokines and the naturally formed blockers is a mystery yet to be unraveled.

However, it is possible that monocyte preactivation might sometimes work to benefit, rather than harm, the patient. In mice rendered tolerant to lipopolysaccharide (via a 14-day course of endotoxin administration), the effects of an infected burn injury were less than those effects in controls [84]. Extrapolating from these findings, we can speculate that monocytes from patients with certain chronic conditions (such as rheumatoid arthritis) may "learn" to tolerate circulating cytokine concentrations, and thus, may not react with excess additional production. This conjecture is purely hypothetical, but may be worth investigating. The same can be said about the relationship between proinflammatory cytokines and the naturally formed anti-inflammatory mediators.

Bone Marrow Stimulation.

Maturation is known to regulate monocyte cytokine production [85]. In patients with SIRS, excessive systemic cytokine production may stimulate the bone marrow and produce marked changes in the types of monocytes produced.

For example, both trauma patients and burn victims have been shown to have an increased proportion of Fc gamma RI^{plus} monocytes [49]. These monocytes have been linked to aberrant monocyte and lymphocyte function, as well as to metabolic derangements [49]. In addition to

expressing a receptor for immunoglobulin G, Fc gamma RI^{plus} monocytes produce increased concentrations of cell-associated TNF, IL-1, and IL-6 [49]. Miller-Graziano et al. [49] suggested that in such patients, a number of infectious and noninfectious stimuli can prompt the disproportionate development of Fc gamma RI^{plus} monocytes during myeloid differentiation. The IL-6 released by these monocytes stimulates lymphocytes to release immunoglobulin G, which, in turn, stimulate the Fc gamma RI^{plus} monocytes to produce even more cytokines. This cascade alters the hormonal milieu even further, making it even more likely that more Fc gamma RI^{plus} monocytes will be released. The net result is a feedback loop that may ultimately overwhelm counterregulatory mechanisms.

Failure To Respond Appropriately to Systemic Cytokines.

When contemplating the development of SIRS, we must consider not only the extent and type of cytokine production, but the effect of that production. For example, in both survivors and nonsurvivors of severe burns, IL-6 concentrations peak 6 hrs after injury [24]. In survivors, IL-6 release is followed by an initial decrease, and then a marked release, of acute-phase proteins [24]. However, in nonsurvivors, the amount of acute-phase protein that is released remains low. There may be a number of as yet unknown mechanisms by which the body is prevented from responding appropriately to cytokines.

Alterations in Cytokine Metabolism.

Even normal concentrations of cytokine production can produce problems if these mediators are not metabolized properly. For example, patients with liver cirrhosis have decreased metabolism (as well as increased production) of TNF and IL-6 [81]. This phenomenon may render patients with liver cirrhosis or other forms of hepatic insufficiency at increased risk of developing SIRS.

Ischemia-Reperfusion Injury.

In rats, serum TNF concentrations increase when induced liver ischemia is followed by reperfusion. Maximum TNF concentrations are obtained 30 mins to 3 hrs after reperfusion [86]. The ischemia-reperfusion injury produces direct hepatic injury (as expected), but it also causes pathologic changes in the lungs [86]. This distal organ involvement suggests that ischemia-reperfusion injury may be another factor that can contribute to the onset of SIRS.

Undoubtedly, there are many other factors that also contribute to the onset of SIRS. However, the examples cited above suggest the extreme complexity of this pathogenic process. The examples also help explain why multiple factors may predict a poor outcome in patients with SIRS. For example, if we accept the proposition that either inappropriately high or inappropriately low cytokine concentrations contribute to the onset of SIRS, then we can better understand why both increased IL-6 concentrations [62,87] and decreased IL-1 concentrations [16] have been associated with a poor outcome. We have yet to learn the kinetic relationship between cytokines and the naturally produced anti-inflammatory mediators.

The persistence of increased cytokine concentrations reflects the body's inability to down-regulate their production or increase their metabolism. In patients with sepsis, it has been shown that survival is unlikely in patients with persistently increased serum TNF and IL-6 concentrations [1,13,87]. However, as the studies cited above demonstrate, the definition of "persistent" may vary depending on the underlying insult and the relationship to anti-inflammatory mediators. Thus, a cytokine concentration that remains increased for weeks may be appropriate in a patient with massive burns, but this situation may be inappropriate in a patient with sepsis, depending on other, yet-to-be investigated relationships.

CONCLUSIONS

Cytokines are found in a wide variety of mammalian species, which raises the question of how (and when) these agents arose in the evolutionary sequence. If we assume that these mediators exert predominantly systemic effects, it would be reasonable to postulate that these agents arose rather late in evolutionary history. However, if we accept the argument that the primary role of cytokines is in the regulation of the local environment, then we must ask if these agents are much more ancient. To my knowledge, cytokines have not been found in nonmammalian species, although this "absence" may be because we have not looked for the cytokines.

Knowing the age of cytokines may have practical significance. Does SIRS represent an evolutionary mechanism to kill off an organism when local wound and infection control has failed? If the answer to this question is "yes," it does not alter our obligation to search for strategies to combat this disorder, but it does change how we think about cytokines and SIRS. Only by fully understanding how these extraordinarily complex proteins work will we be able to develop effective agents that combat their destructive effects while preserving their protective functions.

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