Available online at www.sciencedirect.com
SCIENCE DIRECT
Microbes and Infection 8 (2006) 1382–1389
Microbes and Infection
www.elsevier.com/locate/micinf

Review

The systemic inflammatory response syndrome

Charles M. Robertson, Craig M. Coopersmith*

Department of Surgery, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8109, St. Louis, MO 63110, USA

Available online 23 March 2006

Abstract

The systemic inflammatory response syndrome (SIRS) is the body's response to an infectious or noninfectious insult. Although the definition of SIRS refers to it as an ''inflammatory'' response, it actually has pro- and anti-inflammatory components. This review outlines the pathophysiology of SIRS and highlights potential targets for future therapeutic intervention in patients with this complex entity.

Keywords: Adaptive immune system; Biomarkers; Critical illness; Hyperinflammatory; Hypoinflammatory; Inflammation; Innate immune system; Multiple organ dysfunction syndrome; Pathophysiology; Sepsis; Systemic inflammatory response syndrome

1. Introduction

The official definition of the systemic inflammatory response syndrome (SIRS) is ''the systemic inflammatory response to a variety of severe clinical insults'' manifested by at least two of the following: (a) hyperthermia or hypothermia, (b) tachycardia, (c) tachypnea or hyperventilation, or (d) leukocytosis or leukopenia [1]. Although the sequelae of the body's response to inflammation have long been recognized, SIRS has been formally recognized as a specific entity only since 1992.

1.1. History

Prior to SIRS being defined as a unique syndrome, the effects of severe systemic inflammation on the body were readily observable to clinicians taking care of patients in intensive care units (ICUs). While novel therapeutics resulted in patients surviving diseases that would have resulted in certain death decades earlier, they did not provide instant cures. Rather, if patients ultimately recovered, they did so more slowly, and the body's acute and subacute inflammatory response to previously fatal diseases became apparent. Specifically, advances in medical care of one condition brought to light other problems.

Many of these advances were clustered around the large trauma population associated with wars. During the twentieth century, cardiovascular collapse from hemorrhage was common in World War I, renal failure was common in World War II, and respiratory failure was common during the Vietnam War. Discussing renal failure in World War II, the famed surgeon Edward Churchill noted: ''A chain is only as strong as its weakest link. When links are strengthened where the chain has broken previously, new weak spots appear simply because the chain holds to test them'' [2]. The advent of intravenous fluid resuscitation, blood transfusion, hemodialysis, mechanical ventilation, and vasopressors meant death from failure of a single system became less common but dysfunction in multiple organ systems became more common.

1.2. Definition and shortcoming of the definition

By the end of the twentieth century, a patient could simultaneously tolerate multiple conditions that had been

* Corresponding author. Tel.: +1 314 362 9342; fax: +1 314 362 1602.
E-mail address: coopersmithc@wustl.edu (C.M. Coopersmith).

1286-4579/$ - see front matter © 2006 Elsevier SAS. All rights reserved.
doi:10.1016/j.micinf.2005.12.016

singly fatal two generations earlier. However, these patients had clinical outcomes that were exponentially worse than those with a single organ failure. A desire to understand multiple organ failure (MOF) plus a rapid expansion of the field of critical care medicine led to a consensus conference between the American College of Chest Physicians and the Society of Critical Care Medicine which created a common vocabulary of syndromes facing critically ill patients in order to better understand specific disease entities and improve outcomes. This conference defined numerous disease entities including SIRS, sepsis, severe sepsis, septic shock, bacteremia, and multiple organ dysfunction syndrome (MODS) (Fig. 1).

Unfortunately, the criteria used to diagnose SIRS are very general, requiring abnormalities in temperature, heart rate, respiratory rate, and white blood cell count. As such, the usefulness of the SIRS concept has been widely criticized as being too nonspecific to be of substantial use. A follow-up consensus conference of five major international critical care/infectious disease organizations convened 10 years subsequent to the one that defined SIRS concluded that the entity ''is valid to the extent that a systemic inflammatory response can be triggered by a variety of infectious and noninfectious conditions'' [3]. However, while acknowledging that current medical knowledge and technology precludes a more specific definition, the conferees emphasized the limited utility within the concept of SIRS, since the number of individual disease entities that can lead to a systemic inflammatory response are numerous and frequently divergent. Since there are no specific diagnostic tests and no approved therapeutics directed towards the entity, understanding the pathophysiology underlying SIRS and treating the numerous hospital and ICU patients with SIRS remains a challenging problem.

For simplicity, SIRS can be broken down into two main categories: sepsis and noninfectious inflammation. Sepsis is simply defined as SIRS with infection. SIRS can also be induced by a number of unrelated noninfectious entities. These include burns, pancreatitis, acute respiratory distress syndrome (ARDS), surgery, and trauma.

2. Epidemiology and natural history

The incidence of SIRS is extremely high. It has been estimated that one third of all in-hospital patients, greater than 50% of all ICU patients, and greater than 80% of surgical ICU patients meet the criteria for SIRS [4].

The natural history of SIRS was examined in a landmark study by Rangel-Frausto et al., during a 7-month study of three ICUs and three hospital wards in an academic medical center [5]. Of the 3708 patients admitted, 68% met the criteria for SIRS. Patients with SIRS had a 26% chance of developing sepsis, an 18% chance of developing severe sepsis and a 4% chance of developing septic shock. Not surprisingly, the more SIRS criteria a patient had, the more likely they were to develop sepsis and the more likely they were to develop ARDS, disseminated intravascular coagulation, acute renal failure, and shock. In addition, 50% of patients who met two criteria for SIRS developed a third 7 days later. Mortality was also directly related to the severity of SIRS and whether or not the patient developed septic shock. Patients who had two SIRS criteria on the date of admission had a mortality of 6% (compared to 3% for patients without SIRS), while those with three SIRS criteria had a mortality of 9% and those meeting all four SIRS criteria had a mortality of 18%. This was not substantially different from patients with sepsis or severe sepsis (mortality rates of 16% and 20%, respectively), indicating that infection superimposed on SIRS does not increase mortality unless a patient develops septic shock (where mortality was 46%). The lack of synergy between SIRS and infection was confirmed in a different one-year study of 28 ICUs where mortality from sepsis was similar regardless of whether a patient had SIRS or not [6].

Most longitudinal studies examining SIRS epidemiology and outcome enroll all eligible patients, regardless of the etiology of the syndrome. This is both a strength and a weakness. On the upside, enrolling patients from multiple ICUs minimizes enrollment bias and gives the most complete understanding of the broad population who meet the clinical criteria for SIRS. On the downside, it can be difficult to extract

Systemic Inflammatory Response Syndrome (SIRS): An inflammatory response to a wide variety of clinical insults manifested by two or more of

- temperature >38°C or <36°C
- heart rate >90
- respiratory rate >20 or $PaCO_2$ <32 mm Hg
- WBC count >12K or <4K, or >10% immature (band) forms.

Sepsis: SIRS caused by infection

Severe Sepsis: sepsis with at least one organ dysfunction or hypoperfusion

Septic Shock: severe sepsis associated with hypotension that is resistant to adequate fluid resuscitation

Bacteremia: the presence of viable bacteria in the blood stream

Multiple Organ Dysfunction Syndrome (MODS): impairment of two or more organ systems in an acutely ill patient where homeostasis cannot be maintained without therapeutic intervention

Fig. 1. Consensus definitions of a spectrum of clinical entities that result in organ failure.

data on individual patient populations, based upon the heterogeneity of the syndrome. This is critical because it is unlikely that (for example) septic patients and trauma patients will have entirely similar clinical trajectories or pathophysiology, even if both manifest themselves with fever, tachycardia, tachypnea and leukocytosis.

A complementary approach is to study the natural progression of SIRS in a more focused patient population than "all eligible patients." An example of this is a prospective analysis of the effect of SIRS in 2300 surgical ICU patients over a 49-month period [7]. On admission, half of patients had SIRS, but this dropped to 34.5% of patients who stayed in the SICU 2 days, while the SIRS score decreased 0.8 points a day on average over the first two days, independent of whether the patient's admission was nonoperative, emergent or elective. However, if an individual patient's SIRS score was unchanged or increased between the first and second ICU day, their mortality increased from 11% to 18% to 22%. Thus in this selected patient population, 24 h of aggressive ICU care and resuscitation resulted in a reproducible decrease in the percentage of patients with SIRS, suggesting the diagnosis may be overly sensitive in the SICU. However, in the minority of patients who failed to improve with standard ICU care, day 2 SIRS score (but not day 1 SIRS score) was an independent predictor of death.

3. Challenges to understanding the pathophysiology of SIRS

The first major hurdle to understanding the pathophysiology of SIRS is simply that the terminology is so nonspecific, the syndrome so diffuse, as to render it nearly meaningless in the clinical setting. This problem was highlighted in a recent editorial regarding sepsis, SIRS, MODS and multiple organ failure (MOF) as follows: "Does the concept and definition of SIRS have any relevance…I think not. Everyone who is injured will have SIRS. So what? MODS and MOF are simply descriptions of patients that get in trouble. Thus, SIRS is sick, MODS is sicker and MOF is sickest." [8].

Potentially, an even bigger problem is the fact that the concept of SIRS, in isolation, is incomplete since the unifying theme of patients with two or more SIRS criteria is "an inflammatory response", commonly thought to mean a proinflammatory state. While this may be accurate in a subset of patients (postoperative SICU admissions, for example), it is assuredly not so in the majority of those will eventually die. This is because deaths from overwhelming inflammation are rare. While examples of pure or nearly pure proinflammatory states such as meningococcemia can occur, this is exceedingly rare. Although the degree of inflammation varies between disease state (patients with burns are more catabolic than any other subset with SIRS), in general, the more severe the state of illness and the longer it exists, the more likely it is that a patient will develop immunoparalysis.

Herein lies the difficulty with the utilization of SIRS as either a diagnostic or pathophysiologic entity. In the early stages of critical illness, a number of markers of inflammation (outlined below) are increased. In the later stages, there is a shift toward an anti-inflammatory state. If this is self-limited, patients usually survive. If this does not resolve, patients frequently develop secondary infections and die. Thus, following burn injury T lymphocytes shift from a proinflammatory Th1 phenotype (interferon [IFN]-γ and tumor necrosis factor [TNF]-α producing) to an anti-inflammatory Th2 phenotype (interleukin [IL]-4 and IL-10 producing), and this is associated with worsened survival [9].

The incompleteness of the definition of SIRS as a proinflammatory response was rapidly recognized by those who defined the entity. Within a few years of the initial description of SIRS, multiple studies blocking proinflammatory mediators failed to improve outcome in critically ill patients. This led the conference chairperson that identified SIRS as a unique entity, Roger Bone to state "I believe the model we created had a fundamental flaw: it is one sided. Evidence is accumulating that in response to the original inciting event (the inflammatory response), the body also mounts an anti-inflammatory response," which he dubbed the compensatory anti-inflammatory response syndrome (CARS) [10]. Shortly thereafter, he expanded his definition of SIRS and how it leads to MODS to five stages: local response, initial systemic response, massive systemic inflammation, excessive immunosuppression, and immunologic dissonance where a patient's pathophysiologic response is inappropriate for their biologic needs [11].

4. The immune system and SIRS

While numerous differences exist in the pathophysiology between sepsis and noninfectious inflammation, many of the mechanisms underlying patients with SIRS are similar. SIRS represents the body's *response* to an inciting event (infection, burn, etc), rather than a direct effect of that event. While the end result—a sick or dying patient—is similar, the pathophysiology must be understood in the context of how the host fights against a microbe or injury it considers "bad," and how that response can be perpetuated, even after the inciting event has been eliminated. Ultimately, both the innate and adaptive immune system play a major role in the pathophysiology of SIRS, and both arms interact with each other via crosstalk.

4.1. The innate immune system

The innate immune response is the first line of defense against a microbial invader and represents a nonspecific response that can be activated within minutes. Innate cell types such as neutrophils and macrophages have pattern recognition receptors (PRRs) that recognize diverse molecules known as pathogen-associated molecular patterns (PAMPS). When a PRR recognizes a PAMP, cells of the innate immune system generate a robust response that may ultimately result in the death of invading bacteria. This can be accomplished via phagocytosis or by inducing an upregulation of the immune response.

Specifically, recognition of a PRR by a PAMP can lead to complex intracellular signaling with activation of transcription factors, leading to cytokine generation. An example of this is

binding to Toll-like receptors (TLRs). Ten TLRs have been identified in the human genome, and they can be located at either the cell surface or in the cell's interior [12]. The most well studied of these is TLR4, which recognizes lipopolysaccharide (LPS), a major component of the cell wall of Gram-negative bacteria. When LPS binds TLR4 in the presence of proteins CD14 and MD2, a signal is generated that is transduced by key adapter proteins (of which MyD88 was the first one identified) leading to recruitment of protein kinases including IRAK-4. In turn, this leads to the phosphorylation of IκB and activation of the transcription factor NF-κB. While NF-κB targets greater than 150 genes, a prototypical one in the pathophysiology of SIRS is the early proinflammatory cytokine TNF-α. The complicated role TLR4 plays in sepsis is highlighted by C3H/HeJ mice that have a missense point substitution in the receptor. While fully resistant to LPS-induced injury, these mice actually have increased mortality to authentic sepsis, implying that fully preventing the proinflammatory response may be harmful in sepsis.

In addition to its role in sepsis, TLR4 signaling may play a critical role in noninfectious SIRS as well. While TLR4 is frequently viewed as important exclusively in Gram-negative infections, recent evidence suggests that an endogenous pathway activating SIRS can be induced via TLR4 [13]. Soluble heparan sulfate is a negatively charged glycosaminoglycan that can stimulate TLR4. Injection of this compound and elastase (which cleaves and releases the heparan sulfate proteoglycans) induces a SIRS-like response in mice with intact TLR4 signaling. However, the SIRS response is not observed in either C3H/HeJ mice or TLR4 knockout animals, suggesting the receptor can play a critical role in mediating the SIRS phenotype in the absence of infection.

The severity of SIRS also influences the host's susceptibility to infection via the innate immune system. In a study designed to determine the influence of the inflammatory response on subsequent infection, mice were given low dose cerulein or partial thickness burn (mild SIRS) or high dose cerulein or full thickness burn (severe SIRS) [14]. Animals were then infected with Gram-negative or Gram-positive organisms or given polymicrobial sepsis via cecal ligation and puncture, a model of polymicrobial intra-abdominal sepsis. Mice with severe SIRS were highly susceptible to all infections whereas mice with mild SIRS were resistant compared to unmanipulated mice. SCID mice given peritoneal macrophages from severe SIRS animals died following infection whereas SCID mice given macrophages from mild SIRS animals survived the same infection. Of note, peritoneal macrophages from mild SIRS mice exhibited properties of classically activated macrophages while macrophages from severe SIRS mice had properties of alternatively activated macrophages.

4.2. The adaptive immune system

In contrast to the innate immune system, the adaptive immune system is more specific in defending the host from a wide array of microbes. However, while the targeted response of T and B lymphocytes to unique antigens increases the adaptability of the immune response, it takes substantially longer to develop. Numerous lines of investigation demonstrate that following a proinflammatory state, sepsis is associated with immune suppression associated with changes in the adaptive immune system. As outlined above, CD4 T-helper cells can secrete cytokines with distinct pro- and anti-inflammatory profiles. Although the mechanisms remain to be fully elucidated, a shift from a Th1 to a Th2 profile is commonly seen in SIRS, regardless of whether the insult is infectious or noninfectious (this shift is seen in both trauma and burn patients). Not only is there a shift in the type of cytokines produced, in severe cases, there can also be a shift in the ability of T cells to respond at all when presented with an appropriate antigen. This nonresponsive phenomenon, also known as anergy, has been demonstrated in septic patients with lethal infectious peritonitis. Compared to either healthy controls or septic patients who survived, T cells from nonsurvivors showed markedly depressed Th1 cytokine production without any alteration in Th2 function, consistent with anergy [15].

Increased SIRS-induced apoptosis can also lead to immunosuppression which worsens outcomes, through a mechanism that appears to involve IFN-γ [16]. Both sepsis and noninfectious inflammation induce apoptosis in lymphocytes, the gut epithelium and dendritic cells in human and animal studies [17]. Prevention of cell death in either lymphocytes or the gut epithelium by numerous independent strategies improves outcomes in animal studies of Gram-negative or polymicrobial sepsis [18]. Interestingly, apoptosis prevention does not improve survival in a murine model of noninfectious inflammation, although the reasons underlying the differential response between sepsis and noninfectious inflammation have yet to be determined [19].

Although less well studied since they make up less than 10% of T lymphocytes, γδ T lymphocytes may also play an important role in the pathophysiology of SIRS [20]. A study of 37 patients with SIRS (23 infectious, 14 noninfectious) compared to 27 volunteers demonstrated that patients with SIRS had significantly lower levels of γδ T lymphocytes, although those that are present show significantly greater activation. This descriptive study correlates well with data suggesting γδ T lymphocyte knockout mice have markedly increased mortality following a burn injury that is not lethal in wild-type animals [21] and also have increased mortality following Gram-negative pneumonia.

4.3. Interactions between the innate and adaptive immune system

Although the two arms of the immune system are unique, it is simplistic to view them in isolation. The ability of the nonspecific innate immune system to upregulate the adaptive immune system is well known. Multiple cytokines released from cells of the innate immune system act upon dendritic cells, which alters both their phenotype and function. Activated dendritic cells, in turn, function as antigen presenting cells to lymphocytes. In addition, they release numerous cytokines

(such as IL-12, IL-18 and IL-10) that influence the T-cell response.

The crosstalk also moves in the opposite direction. While the ability of T-lymphocyte subsets (especially T regulatory cells) to feed back upon the innate immune system is well described, the importance of this in SIRS has only recently begun to be examined. A major study on how the adaptive immune system feeds back on the innate immune system in noninfectious SIRS was recently demonstrated in a murine burn model [22]. Typically, a 25% body surface area burn primes innate immune cells to yield increased proinflammatory cytokine production (mediated via TLR4 and TLR2). This phenotype is exaggerated in Rag mice that lack T lymphocytes, demonstrating how the adaptive immune system can feed back on the innate system. While the mechanisms underlying this feedback remain to be fully delineated, the critical cell type appears to be the CD4+CD25+ (T regulatory) cell. Specifically, experiments with T lymphocyte subset knockouts demonstrated that the burn-induced proinflammatory cytokine production changes are due a CD4+ but not CD8+ mediated phenomenon. Further separation of CD4+ cells in CD25+ and CD25− subset demonstrated that only CD4+CD25+ cells reduced TLR-stimulated cytokine production to levels seen in wild-type mice.

4.4. A comprehensive theory of the immune response in critical illness

A generalized theory of the activity of the immune system in sepsis was recently proposed by Hotchkiss and Karl (Fig. 2) [23]. According to this hypothesis, patients initially have a hyperinflammatory response. The severity of this response is multifactorial, dependent upon factors intrinsic to the host and those extrinsic to the host. Host-specific factors include genetics as well as age, gender, and co-morbid conditions. Host-independent factors include the virulence of the organism and size of the inoculum. Of note, while the published theory is specific for sepsis, it easily adaptable to noninfectious SIRS. For patients with SIRS in the absence of an infection, the host-specific factors are unchanged while the host-independent factors are injury specific. For instance, in a burn patient, instead of organisms/inoculum factors, the percent body surface area burn and depth of the burn would help determine the severity of the proinflammatory response.

Following the initial hyperinflammatory response, a secondary hyperinflammatory response can occur due to a secondary infection. Once again, this hypothesis can be extended to include noninfectious inflammation as a secondary cause of hyperinflammation, as would be seen in a hospitalized patient who developed ARDS after their initial insult. During this time, proinflammatory cytokines would be markedly elevated, and treating a patient with an anti-inflammatory agent would theoretically be beneficial.

In patients whose infection (or injury) resolves, there is only a minimal anti-inflammatory response. However, in patients with infections (or injuries) that do not resolve quickly and/or in patients with multiple co-morbidities, the hyperinflammatory state is transient, and is followed by a longer hypoinflammatory state. Whether or not a patient recovers or dies is again dependent on intrinsic (ability of host to reverse their anergic state) and extrinsic factors (if surgery is needed for source control of infection or to graft burned areas). In patients who recover, the hypoinflammatory state is slowly reversed, although clinically this process can take weeks to months. Alternatively, if the hypoinflammatory response is not reversed, the patient progresses towards MODS and then MOF. Ultimately, the immune system is unable to mount the necessary response, solid organs cease to function despite exogenous support (potentially due to cell hibernation), and an irreversible state is reached that culminates in the patient's death.

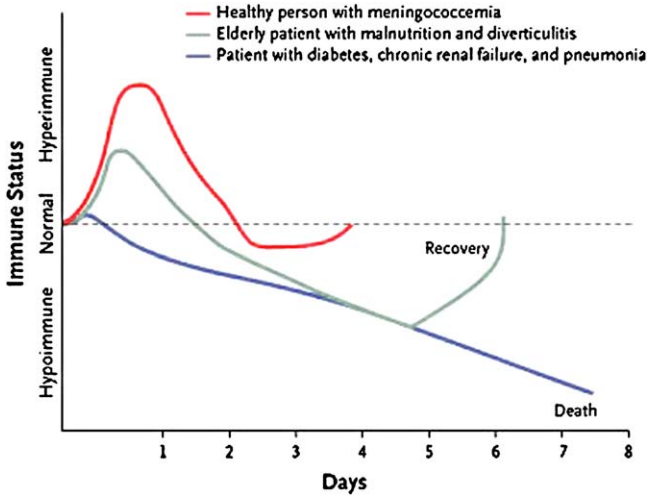

Fig. 2. Immunologic response of three hypothetical patients with infectious SIRS. The host response is dependent upon patient-specific factors and patient-independent factors. In the top curve, the young healthy patient with meningococcemia has a predominantly proinflammatory response. The patient will either recover with a minimal anti-inflammatory response or die. This is the clinical situation where an anti-inflammatory agent might be beneficial. In keeping with their pre-existing medical conditions, the other two patients have less of a proinflammatory response, with the bottom (sickest at baseline) patient having almost exclusively an anti-inflammatory response. The hypoinflammatory response will either improve in these patients with recovery or the patients will ultimately die. Although these hypothetical responses were initially proposed for sepsis, similar trajectories can be seen in noninfectious SIRS. Source: Hotchkiss and Karl [23] (Copyright 2003, Massachusetts Medical Society. All rights reserved).

5. Mediators and markers of SIRS

Implicit within the Hotchkiss and Karl theory of critical illness is that there are factors that cannot be altered (one's age, genetics and pre-morbid conditions), and there is a time when initiating therapy is too late. Further, the type of therapy needed is different depending on the patient's immune status at the time treatment is initiated. For instance, treating a patient with an anti-inflammatory agent makes sense only if a patient is in the narrow time window that they are hyperinflammatory. There is certainly no "magic bullet" towards treating SIRS due to the multi-factorial nature of inciting agents, the

heterogeneity of those who develop SIRS, and the varied immune trajectories of those who have SIRS. However, a number of mediators have recently been identified that may play a critical role in the pathophysiology of the disease. Some of these mediators may be candidates for therapeutic intervention if appropriately targeted to the correct patient population at the correct disease stage. In addition, since SIRS is a nonspecific entity, biomarkers may be useful towards identifying the outcomes of specific subsets of patients who carry the diagnosis.

5.1. Chemokine receptors

Chemokines are small, secreted proteins that bind receptors that, in turn, activate neutrophils and macrophages as well as both the endothelium and the epithelium. The chemokine receptors CXCR1 and CXCR2 (the receptor for IL-8) are potential therapeutic targets in sepsis. This is evidenced by the fact that CXCR2 knockout mice have substantially improved outcomes compared to wild-type mice following cecal ligation and puncture. In addition, inhibitors of these agents can prevent ischemia/reperfusion or lung injury.

A new approach to manipulate this clinically was the development of pepducins, cell-penetrating lipoproteins that target chemokine receptors. Pepducins derived from the i1 or i3 intracellular loops of CXCR1 and CXCR2 were recently described [24]. Daily injections (for 6 days) of pepducins against CXCR1 and CXCR2 begun immediately after CLP decreased mortality from 100% to 3%. When pepducin injections were started 8 h following CLP, mortality was still decreased from 100% to 13%. This was associated with a decrease in the SIRS response of mice and a prevention of multiple organ failure. Of note, pepducins selective for CXCR4 (which is important in lymphocyte homing and cancer but has not been shown to have a definitive role in inflammation) induced leukocytosis without impacting survival.

5.2. Macrophage migration inhibitory factor

Macrophage migration inhibitory factor (MIF) is a potent regulator of the innate immune system [25]. MIF is a constitutively expressed cytokine present on most cells in the immune system as well as in epithelial cells that contact the host's natural environment. Unlike most cytokines, MIF is stored in intracellular pools and so does not require protein synthesis prior to secretion. MIF mediates both inflammation and infection through a number of routes including upregulating TLR4 expression by macrophages, activating ERK1/ERK2 signaling, suppressing p53 activity and inhibiting JAB1 activity.

Human studies comparing MIF levels in both patients with SIRS and healthy volunteers demonstrate that MIF levels are substantially higher in patients who do not survive SIRS than those with the entity who survive (or controls). MIF is also upregulated in patients with ARDS. While this data is associative, numerous animal studies suggest MIF plays an important role in the pathophysiology of SIRS of both infectious and noninfectious etiologies. First, mice given MIF have increased mortality following either Gram-negative sepsis or noninfectious inflammation. Next, MIF knockout mice are resistant to both LPS and staphylococcal enterotoxin B, and anti-MIF antibody improves survival in both lethal bacterial sepsis (monomicrobial or polymicrobial) as well as that induced by Gram-positive-induced superantigens. Of note, MIF does not act through TNF-α since anti-MIF antibodies are still protective in TNF-α knockout mice.

5.3. Biomarkers

Multiple biomarkers with varying degrees of sensitivity and specificity have been demonstrated to be elevated in sepsis (and less commonly in noninfectious SIRS) including IL-6, procalcitonin (PCT), C-reactive protein (CRP), adrenomedullin, soluble ELAM-1, soluble CD14, MIP-1α, mannose binding lectin, and extracellular phospholipase A_2. While a full description of each of these is outside the scope of this review, a few biomarkers have been shown to be elevated in multiple studies of SIRS (both infectious and noninfectious), and therefore merit special consideration. IL-6 levels are elevated in patients with ARDS or septic shock and may be useful in predicting outcomes in patients with these diseases. IL-6 levels as well as PCT levels have also been demonstrated to be markers of subsequent SIRS and/or sepsis in patients undergoing elective cancer resections [26]. Further, the ratio of IL-6 to IL-10 has been shown to be predictive of outcome in patients with SIRS, regardless of etiology. A recent study of 40 patients with shock from infectious SIRS demonstrated that admission IL-6 levels are similar between survivors and nonsurvivors, but that mean IL-6 levels are higher in nonsurvivors [27]. Since IL-6 levels can be obtained within 30 min of blood draw by chemiluminescent enzyme immunoassays, information obtained may be rapidly used for prognostic purposes.

Most biomarker analyses look at a specific subset of patients with SIRS (i.e. postoperative patients or septic patients) and compare them to control. However, a recent study of 150 ICU patients compared PCT and CRP levels in patients with noninfectious SIRS, infectious SIRS (sepsis, severe sepsis and septic shock), or no evidence of SIRS [28]. Both PCT and CRP levels were elevated in patients with SIRS with PCT levels rising more rapidly. Peak levels of each were correlated to severity of organ dysfunction. However, concentrations of both markers were higher in infected patients suggesting that infection superimposed on inflammation may alter pathophysiology to some degree.

6. Therapy

Defining optimal treatment for SIRS in the clinical setting is complicated by the heterogeneity of the entity since the diseases that cause SIRS are disparate and present in a markedly diverse population. For example, amongst noninfectious causes of SIRS, severe pancreatitis is commonly seen in middle aged patients with a history of alcohol abuse, trauma is largely a disease of young men, children are over-represented

among burn patients, and ARDS is more common in elderly patients. For SIRS caused by infection, the spectrum is equally broad in terms of etiology (Gram-positive, Gram-negative, fungal, viral) and host presentation. For instance, a previously healthy pediatric patient with meningococcemia, a middle-aged immunosuppressed liver transplant patient with an opportunistic infection and an elderly patient with multiple co-morbidities who develops community acquired pneumonia all have infectious SIRS.

While a comprehensive overview of therapy is outside the scope of this review, there are some common elements of treatment, regardless of the disease that led the patient to develop SIRS. In general, therapy is supportive. Most patients with SIRS end up in the ICU, where they frequently receive fluid resuscitation, mechanical ventilation, pressor or inotropic support, blood transfusions, renal replacement therapy, etc. While each of these can be life saving, none of these are specific towards any type of critical illness. To date, while numerous mediator-based therapies have proven effective in animal trials of SIRS, none has been demonstrated to be beneficial at the bedside.

In addition to supportive therapy, the inciting agent that resulted in SIRS needs to be treated if one can be identified. Since SIRS represents the body's response to a clinical insult, the initiating insult itself must be treated. For SIRS with septic shock, this means antibiotic therapy, source control (if needed), as well as adjunctive therapies such as activated protein C and low dose steroids [29]. For burn injury, therapy includes early wound debridement and skin grafting.

In addition, further injury must be avoided. For instance, high tidal volumes result in increased mortality in ARDS by inducing both local barotrauma and increased systemic inflammation [30]. While ventilating patients with low tidal ventilation does not cure ARDS, it minimizes additional injury, giving the body a chance to heal from the insult that initially induced lung injury.

7. Conclusions

SIRS represents the body's response to a variety of clinical insults. The name is only partially accurate since patients who develop SIRS have both an initial proinflammatory state and a later anti-inflammatory state. The pathophysiology of SIRS is highly complex, as might be expected in a nonspecific entity that can occur in patients of all ages and co-morbidities with multiple disease states. Despite the heterogeneity of SIRS, it is known that both the innate and adaptive immune system play a critical role in SIRS, and further understanding of the mechanisms involved may allow therapeutic intervention prior to the development of MOF. For now, there is no specific therapy for this nonspecific entity. Since patients are more likely to die while they are hypoimmune, anti-inflammatory agents have not proven to be successful in the treatment of SIRS, and patients are best treated with a combination of supportive care and therapy aimed at the insult that initiated SIRS.

Acknowledgements

This study was supported by funding from the National Institutes of Health (GM66202, GM072808). Many important original publications were either cited in reviews or not cited at all due to limitations on the number of references allowed. We apologize to all researchers who have contributed to the understanding of this vast topic who we were unable to cite.

References

[1] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, Crit. Care Med. 20 (1992) 864–874.
[2] E.D. Churchill, Surgeon to Soldiers: Diary and Records of the Surgical Consultant, Allied Force Headquarters, World War II, Lippincott, 1972.
[3] M.M. Levy, M.P. Fink, J.C. Marshall, E. Abraham, D. Angus, D. Cook, J. Cohen, S.M. Opal, J.L. Vincent, G. Ramsay, 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference, Crit. Care Med. 31 (2003) 1250–1256.
[4] C. Brun-Buisson, The epidemiology of the systemic inflammatory response, Intensive Care Med. 26 (2000) S64–S74.
[5] M.S. Rangel-Frausto, D. Pittet, M. Costigan, T. Hwang, C.S. Davis, R.P. Wenzel, The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study, JAMA 273 (1995) 117–123.
[6] C. Alberti, C. Brun-Buisson, S.V. Goodman, D. Guidici, J. Granton, R. Moreno, M. Smithies, O. Thomas, A. Artigas, J.R. Le Gall, Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients, Am. J. Respir. Crit. Care Med. 168 (2003) 77–84.
[7] M. Talmor, L. Hydo, P.S. Barie, Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: effect of intensive care unit resuscitation, Arch. Surg. 134 (1999) 81–87.
[8] A.E. Baue, Sepsis, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, and multiple organ failure: are trauma surgeons lumpers or splitters? J. Trauma. 55 (2003) 997–998.
[9] J.A. Lederer, M.L. Rodrick, J.A. Mannick, The effects of injury on the adaptive immune response, Shock 11 (1999) 153–159.
[10] R.C. Bone, Sir Isaac Newton, sepsis, SIRS, and CARS, Crit. Care Med. 24 (1996) 1125–1128.
[11] R.C. Bone, Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS), Ann. Intern. Med. 125 (1996) 680–687.
[12] B. Beutler, K. Hoebe, P. Georgel, K. Tabeta, X. Du, genetic analysis of innate immunity: TIR adapter proteins in innate and adaptive immune responses, Microbes Infect 6 (2004) 1374–1381.
[13] G.B. Johnson, G.J. Brunn, J.L. Platt, Cutting edge: an endogenous pathway to systemic inflammatory response syndrome (SIRS)-like reactions through toll-like receptor 4, J. Immunol. 172 (2004) 20–24.
[14] H. Takahashi, Y. Tsuda, D. Takeuchi, M. Kobayashi, D.N. Herndon, F. Suzuki, Influence of systemic inflammatory response syndrome on host resistance against bacterial infections, Crit. Care Med. 32 (2004) 1879–1885.
[15] C.D. Heidecke, T. Hensler, H. Weighardt, N. Zantl, H. Wagner, J.R. Siewert, B. Holzmann, Selective defects of T lymphocyte function in patients with lethal intraabdominal infection, Am. J. Surg. 178 (1999) 288–292.
[16] R.S. Hotchkiss, K.C. Chang, M.H. Grayson, K.W. Tinsley, B.S. Dunne, C.G. Davis, D.F. Osborne, I.E. Karl, Adoptive transfer of apoptotic splenocytes worsens survival, whereas adoptive transfer of necrotic

splenocytes improves survival in sepsis, Proc. Natl. Acad. Sci. U.S.A. 100 (2003) 6724–6729.
[17] R.S. Hotchkiss, P.E. Swanson, B.D. Freeman, K.W. Tinsley, J.P. Cobb, G.M. Matuschak, T.G. Buchman, I.E. Karl, Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction, Crit. Care Med. 27 (1999) 1230–1251.
[18] C.M. Coopersmith, P.E. Stromberg, W.M. Dunne, C.G. Davis, D.M. Amiot, T.G. Buchman, I.E. Karl, R.S. Hotchkiss, Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis, JAMA 287 (2002) 1716–1721.
[19] K.D. Husain, P.E. Stromberg, P. Javadi, T.G. Buchman, I.E. Karl, R.S. Hotchkiss, C.M. Coopersmith, BCL-2 inhibits gut epithelial apoptosis induced by acute lung injury in mice but has no effect on survival, Shock 20 (2003) 437–443.
[20] A. Matsushima, H. Ogura, K. Fujita, T. Koh, H. Tanaka, Y. Sumi, K. Yoshiya, H. Hosotsubo, Y. Kuwagata, T. Shimazu, H. Sugimoto, Early activation of gammadelta T lymphocytes in patients with severe systemic inflammatory response syndrome, Shock 22 (2004) 11–15.
[21] M.G. Schwacha, A. Ayala, I.H. Chaudry, Insights into the role of gammadelta T lymphocytes in the immunopathogenic response to thermal injury, J. Leukoc. Biol. 67 (2000) 644–650.
[22] T.J. Murphy, N.N. Choileain, Y. Zang, J.A. Mannick, J.A. Lederer, CD4+ CD25+ Regulatory T cells control innate immune reactivity after injury, J. Immunol. 174 (2005) 2957–2963.
[23] R.S. Hotchkiss, I.E. Karl, The pathophysiology and treatment of sepsis, N. Engl. J. Med. 348 (2003) 138–150.
[24] N.C. Kaneider, A. Agarwal, A.J. Leger, A. Kuliopulos, Reversing systemic inflammatory response syndrome with chemokine receptor pepducins, Nat. Med. 11 (2005) 661–665.
[25] T. Calandra, T. Roger, Macrophage migration inhibitory factor: a regulator of innate immunity, Nat. Rev. Immunol. 3 (2003) 791–800.
[26] D. Mokart, M. Merlin, A. Sannini, J.P. Brun, J.R. Delpero, G. Houvenaeghel, V. Moutardier, J.L. Blache, Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery, Br. J. Anaesth. 94 (2005) 767–773.
[27] S. Oda, H. Hirasawa, H. Shiga, K. Nakanishi, K. Matsuda, M. Nakamua, Sequential measurement of IL-6 blood levels in patients with systemic inflammatory response syndrome (SIRS)/sepsis, Cytokine 29 (2005) 169–175.
[28] G.P. Castelli, C. Pognani, M. Meisner, A. Stuani, D. Bellomi, L. Sgarbi, Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction, Crit. Care 8 (2004) R234–R242.
[29] R.P. Dellinger, J.M. Carlet, H. Masur, H. Gerlach, T. Calandra, J. Cohen, J. Gea-Banacloche, D. Keh, J.C. Marshall, M.M. Parker, G. Ramsay, J.L. Zimmerman, J.L. Vincent, M.M. Levy, Surviving sepsis campaign guidelines for management of severe sepsis and septic shock, Crit. Care Med. 32 (2004) 858–873.
[30] Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network, N. Engl. J. Med. 342 (2000) 1301–1308.