Update on the Immunological Pathway of Negative Regulation in Acute Insults and Sepsis

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Sepsis with subsequent multiple organ dysfunction is a distinctly systemic inflammatory response to concealed or known infection and is a leading cause of death in intensive care units. In the initial stage of sepsis, a phase of immune activation can be evident, but a marked apoptosis-induced depletion of lymphocytes and a nonspecific anergy of immune function after severe trauma and burns might be responsible for the increased susceptibility of the host to subsequent septic complications. Recent studies indicated that negative regulation of immune function plays a pivotal role in the maintenance of peripheral homeostasis and regulation of immune responses; therefore, an understanding of the basic pathways might give rise to novel insights into the mechanisms of sepsis and immune homeostasis. This review is an attempt to provide a summary of the different pathways of negative regulation that are involved in the pathogenesis of sepsis, secondary to acute insults.

Introduction

SEPSIS DENOTES A COMPLEX clinical syndrome that results from a harmful or damaging host response to infection. Many of the components of the innate immune response that are normally related to host defenses against infection can, under some circumstances, cause cell- and tissue damage resulting in multiple organ failure, which is the end result of sepsis (Yao and others 1998; Cohen 2002). As a result of a concerted effort to disclose the underlying pathogenetic mechanisms, there have been accumulating evidences to suggest that the profound pro-inflammatory and anti-inflammatory response that occur in sepsis is balanced by an array of counter-regulatory molecules involved in an effort to restore immunological equilibrium. To date, the mechanism of negative regulation has been revealed to play an important role in the physiopathologic process of sepsis, secondary to acute insults. At the initial stage of sepsis, there is a release of large quantities of pro-inflammatory mediators, including tumor necrosis factor (TNF)- α , interferon (IFN)- γ , and interleukin (IL)-2, however, with the progression of disease condition, the immune negative regulation would be elicited, and the reproductive activity of lymphocytes would be inhibited. Further, the initiation of immunological reaction mediated by T helper cell (Th) 2 cells and accompanied by apoptosis of a large number of lymphocytes might lead to an increase in susceptibility to infection.

This article is a brief overview of our understanding concerning the different pathways of negative regulation, to

highlight recent investigations on the role of negative regulation pathways in the induction, maintenance, and function of immunological cells. In addition, we will try to elucidate the pathogenesis of immune disorder to provide new conceptions for early diagnosis and rational treatment of severe sepsis.

Negative Regulation of Immunity by Different Cells Involved in Acute Insults and Sepsis

Naïve CD4 cells may differentiate into different T lymphocyte lineages that possess distinct biologic functions after being activated by various cytokines (Korn and others 2009). There is a growing body of evidence to show that there are cells from patients with sepsis or insults that are able to reduce levels of pro-inflammatory cytokines, but increased levels of anti-inflammatory cytokines and reversal of the Th2 response improves survival among patients with sepsis, such as regulatory T cells (Treg), regulatory dendritic cells (DCs), $\gamma\delta$ -T cells, natural killer T cells (NK-T), and regulatory B cells (Table 1).

Regulatory T cells

Effector CD4⁺ Th cells have been historically classified into Th1 and Th2, depending on the signature cytokines they produce. Recently, a third subset of IL-17-producing CD4⁺ Th cells, called Th17 cells, has been discovered and characterized. Th17 cells also secrete IL-22 to induce series of tissue

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TABLE 1. CHARACTERISTIC FEATURES OF DIFFERENT CELLS IN NEGATIVE REGULATION OF IMMUNITY

Characteristic properties	Different cell subsets				
	Treg	Regulatory DC	Regulatory B cells	$\Gamma\delta$ T cells	iNKT cells
Signature cytokines	TGF- β	IL-10	TGF- β IL-10 IL-6	IFN- γ	IL-4 IL-2
Additional cytokines produced	IL-10 IL-35	TNF- α	IL-4	IL-4	IFN- γ
Primary signaling regulators	JAK-STAT	MAPK	P38/ERK1/2	TLR2 TLR3 TLR5	NF- κ B
Cytokine/chemokine/specific antigen receptor	CD25 (IL2R α)	CCR1 CCR2 CCR5 CXCR1 CXCR2 CXCR5	CD45Ro	CCR9	CD1d
Associated diseases	IPEX-like/SCID (CD25/IL2R α deficiency) IPEX (FOXP3 deficiency)	SIRS/MODS	Multiple sclerosis/ Type I diabetes/ Rheumatoid arthritis	Infections and tumors	Inflammation/ HIV-1 interfere with CD1d

DC, dendritic cells; IL, interleukin; IFN- γ , interferon- γ ; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α ; Treg, regulatory T cells; P38, mitogen-activated protein kinase P38; ERK, extracellular signal-regulated kinase; JAK-STAT, janus kinase-signal transducer and activator of transcription; NF- κ B, nuclear factor- κ B; CD1d, major histocompatibility complex class I-related glycoprotein; SIRS, systemic inflammation response syndrome; MODS, multiple organ dysfunction syndrome; MAPK, mitogen activated protein kinase.

reactions. The reciprocal differentiation of Th17 cells and Tregs is closely related, since both of them need transforming growth factor- β (TGF- β), which induces differentiation of Th17 cells and Tregs. Tregs as professional suppressive subsets of CD4 cells, play a pivotal role not only in immune homeostasis, transplantation tolerance, tumor immune evasion, and suppression of allergic response, but also in the regulation of immune responses to infectious pathogen (Mellor and others 2005). There are many types of Tregs, classified according to their development, specificity, and role of action, and they can be divided into naturally occurring Tregs and induced Tregs. Generally, naturally occurring Tregs become mature in the thymus and then enter the peripheral lymphoid tissue. A growing body of studies suggests that a small population of CD4⁺CD25⁺ Treg is responsible for immunoregulation (Baecher-Allan and others 2002). Induced Tregs [iTregs, TGF- β -induced Foxp3-expressing Tregs, from naïve CD4 cells] is a group of mature T cells (CD4⁺CD25⁺ T cells) situated in peripheral lymphoid tissues and formed when antigen-experienced T lymphocytes (CD4⁺CD25⁺ lymphocytes) are exposed to specific antigen or immunosuppressive cytokines, activated under the action of induction (Table 1), including TGF- β -producing Th3 cells (Bach 2003; Yi and others 2006; Zou 2006) and IL-10-producing T regulatory type 1 (Tr1) cells (Ochs and others 2009). The immune regulatory mechanisms of Treg mainly contribute to immunosuppression and immune nonreactivity (Asano and others 1996; Sakaguchi and others 2006).

Treg-mediated suppressive effect of immune function and the imbalance of T-cell differentiation. Under the circumstance of normal immune response or no-inflammatory injury, Th1 and Th2 subsets are in balance. Treg-mediated immunosuppressive effect is derived from the drift of Th1/Th2 caused by the activation of T cell receptor (TCR) signal. Data

are accumulating to suggest that CD4⁺ T cells stimulated by various cytokines and co-stimulating molecules can be induced to differentiate into different effector T cells, including the production of large quantities of IFN- γ by Th1, and IL-4 and IL-10 by Th2 (Iwasaka and Noguchi 2004; Akdis 2006; Larche and others 2006; Akdis and Akdis 2007). Th1 cells are involved in cell-mediated immunity, activate macrophages and are highly effective in clearing intracellular pathogens; Th2 cells, on the other hand, mainly participate in humoral immunity, and they may also induce B-cell proliferation and antibody production, allowing deactivation of macrophages and secretion of anti-inflammatory mediators such as IL-4 and IL-10, to prevent the development of uncontrolled inflammation leading to tissue damage. Th2 cells have the capability to downregulate the synthesis of pro-inflammatory cytokines, contributing to degrading of local inflammatory mediators, and they play important roles in maintaining the balance of autoimmunity and contribute to an important element in negative regulation (Mosmann and Coffman 1989). MacConmara and others (2006) observed that the inhibitory capacity of Tregs was reinforced in patients 7 days after injury compared with normal control group, and this might be the result of differentiation of CD4⁺ T cells to Th2 cells, at the same time, cytokine production of Th1 as an influence of Treg, and production of anti-inflammatory cytokines (IL-10) that induce the differentiation. During experimental and clinical sepsis, an increasing percentage of Tregs has been observed and expansion/conversion of Tregs was examined in the postseptic immune system. Data show that augmented Treg expansion and function obstruct tumor immunosurveillance in the postseptic immune system, indicating that Tregs may also have a crucial inhibitory effect on the antitumor immune response (Cavassani and others 2010).

Patients with sepsis have features consistent with immunosuppression, including more differentiation of CD4⁺

T cells into Th2 cells, an increase in anti-inflammatory mediators in the peripheral blood accelerating a decrease in pro-inflammatory cytokine, resulting in an imbalance between pro-inflammatory and anti-inflammatory response. It is clear now that Th1 clones synthesize IL-2, IFN- γ , and lymphotoxin, whereas these lymphokines are not detectably expressed in Th2 clones; conversely, only Th2 clones synthesize detectable amounts of IL-4 and IL-10 (Cherwinski and others 1987). However, there is preferential activation of Th2 cells in the development of sepsis, under the condition, and levels of Th2 cytokines (IL-4 and IL-10) increase and levels of pro-inflammatory mediators decrease, which would lead to immunologic derangement (Huang and others 2009, 2010). The balance of immune response can be regulated through Th1/Th2 polarization, while the determinative factors of the drift of Th1/Th2 mediated by Treg is not clear. There are various factors that may be involved in this process, including the species of pathogen, different development stage of inflammation, and cytokines in infected sites.

In a previous study, the results showed that expression of CD152 (cytotoxic T-lymphocyte-associated antigen 4, CTLA-4) and forkhead/winged helix transcription factor p3 (Foxp3) was strongly upregulated in splenic Tregs on post-burn days 1–7, in comparison to those from sham-injured rats (Huang and others 2009). To verify whether the activation of Tregs was associated with excessive production of high mobility group box-1 protein (HMGB1), a late mediator of sepsis, after burn injury, ethyl pyruvate was used to inhibit the effect of HMGB1. It was found that treatment with ethyl pyruvate could dramatically decrease the expression of CD152, Foxp3 on Tregs, and IL-10 production after major burns. However, T-cell proliferative activity and expression levels of IL-2 and IL-2R α were markedly restored, and T cells were shifted to Th1. These data suggested that excessive release of HMGB1 might stimulate splenic Tregs to maturation and further mediate immunosuppression of T lymphocytes (Huang and others 2009; Yao and others 2009).

Treg-mediated immune nonreactivity and apoptosis. During the process of immunologic derangement in sepsis, on one hand, there is disequilibrium between pro-inflammatory and anti-inflammatory response, with shifting of pro-inflammatory mediators toward anti-inflammatory mediators. On the other hand, there is a persistent increase in activation of Treg, intensifying a state of immune nonreactivity (Sakaguchi and others 1995; Suri-Payer and others 1998; Belkaid and others 2002; Shevach 2002; Hesse and others 2004), including non-reactivity to the antigenic stimulation and a cease of IL-2 production. Even with the presence of a large amount of IL-2, CD4⁺CD25⁺ Treg would be activated and proliferated, though the extent of proliferation is much lower than that of CD4⁺CD25⁻T cells. In addition to immune nonreactivity, apoptotic cell death may trigger sepsis-induced anergy, and recent work has shown that cells can die by apoptosis. Treg can induce apoptosis of autoreactive thymic T cells through a mechanism involving the Fas/FasL pathway (Venet and others 2006), the contributory mechanism of which is the binding of FasL and Fas, resulting in activation of cysteinyl aspartate-specific protease (caspase)-8. Moreover, the combination of FasL and Fas provokes an increasing production of mitochondrial chromocyte C, which activates the signal transduction pathway of caspase-8 promoting apoptosis. Taken together, these studies supported the assumption that

apoptosis mediated by Fas removes the activated peripheral CD4⁺ T cells, and the Fas pathway also mediates cytotoxic T lymphocytes and NK cells in removing virus infected cells and cancer cells (Mellor and others 2005).

Regulatory (tolerogenic) DCs

DCs are considered as promoters of the immunologic system, and are extensively present in lymphoid- and non-lymphoid tissues. DCs are professional antigen-presenting cells specialized in the capture, processing, and transport of the antigen to lymphoid organs from the secondary lymphoid tissue (Banchereau and Steinman 1998). During this process, DCs also play important roles in monitoring the diversity of internal environment caused by microorganisms, cell damage, hypoxia, and ischemia-reperfusion (Steinman and Banchereau 2007). On the condition of different factors, DCs present diverse functions in implementing the biological effect. DC apoptosis have been observed in the development of sepsis, and it was demonstrated that the specific uptake of apoptotic DC converted immature viable DC into tolerogenic DC, which were resistant to lipopolysaccharide (LPS)-induced maturation (Kushwah and others 2010) and has the ability to induce the differentiation of a distinct subset of Treg (Wakkach and others 2001). When pathogenic microorganisms and organ lesions activate nonspecific immune system, DCs not only present foreign antigen and homo-antigen, but also activate effector T lymphocytes and induce the proliferation of Treg. However, DCs remain immature and tissue resident, and express low amounts of major histocompatibility complex class (MHC) II molecules and negative costimulatory molecules (CD80, CD86), a condition that the ratio of immature DCs increases attended with time lapse, which suggests that the production of Treg or effector T lymphocytes induced by DCs depend on the immature status, referring to the ratio of immature DCs and mature DCs. Compared with mature DCs, the population of immature DCs can present with a low expression CD11c and a high expression of CD45RB, additionally, and it can express low amounts of costimulatory molecules (CD80, CD86, and MHC II), characterized by the appearance of plasmacytoid and immature phenotype, and secretion of high IL-10 levels after activation (Moore and others 2001; Wakkach and others 2003). These regulatory DCs can be derived from bone marrow cells in the presence of granulocyte-macrophage colony-stimulating factor, TNF- α , and IL-10, and they secrete high levels of IL-10 following activation, and induce T-regulator type 1 cells both *in vivo* and *in vitro* (Fujita and others 2006, 2008). A previous study demonstrates the ability of IL-10 to induce the differentiation of distinct subsets of DCs that specifically express the CD45RB marker and secrete IL-10. On the contrary, IL-10 could be one of the maturation signals and promote the differentiation of DCs, at the same time IL-10 inhibits the expression of cytokines secreted by Th1 cells (Akdis and Akdis 2007). Accordingly, cytokines released by regulatory DCs may affect the immunological activity, thereby exerting immunoregulatory effects. Recent studies have revealed that these regulatory DCs generated *in vitro* by culturing bone marrow cells obtained from mice protected against septic response to microbial pathogens in innate immunity (Fujita and others 2006). Likewise, we reported that as a subset of naturally existing DC, CD11c^{low}CD45RB^{high} DCs were presented in the spleen and

could protect mice from acute inflammatory response after thermal injury (Liu and others 2011). Sepsis was associated with a loss of resident DC in the bone marrow; however, in response to polymicrobial sepsis, DC precursor cells in the bone marrow developed into regulatory DC that impaired Th1 priming and NK cell activity and mediated immunosuppression. Therefore, after sepsis, the absence of DC in the bone marrow might have contributed to the modulation of DC differentiation (Pastille and others 2011).

$\gamma\delta$ -T cells and NK-T cells

$\gamma\delta$ -T cells and NK-T cells are mainly distributed in mucous membranes and lymphoid tissue, but only small numbers in blood, spleen, or peripheral lymph-nodes. Both of these cells play central roles in the postburn survival, cytokine formation by Th1 and Th2 cells, initiation of neutrophil-mediated tissue damage, and wound healing (Schwacha and others 2000; Toth and others 2004; Daniel and others 2007; Pastille and others 2011). Recent experimental studies support the view that $\gamma\delta$ -T cells and NK-T cells may play an important role in the initiation and regulation of the inflammatory and immune cascades induced by burn injury. The previous studies evaluating most $\gamma\delta$ -T cells had a phenotype of spontaneous activation with a rapid turnover rate (Tough and Sprent 1998), and they quickly expanded upon inflammatory activation (Mombaerts and others 1993; Moore and others 2000). $\gamma\delta$ -T cells also influence other T-cell functions through regulation of their cytokine responses (Gao and others 2003). In the setting of major burns, $CD8^+CD11b^+$ $\gamma\delta$ -T cells are present in more numbers in splenic tissue, and also inhibit the lymphocytic proliferation; in contrast to $\gamma\delta$ -T cells, $CD8^+CD11b^+$ $\gamma\delta$ -T cells mainly secrete Th2 cytokine, and the retransfusion of these cells to normal mouse can increase the susceptibility to septic challenge. Invariant natural killer T (iNKT) cells are a subset of T lymphocytes that react with glycolipid antigens presented by the MHC I-related glycoprotein CD1d; they produce copious amounts of cytokines after TCR engagement (Taniguchi and others 2003; Brigl and Brenner 2004; Bendelac and others 2007), including IL-2, IL-4, and IFN- γ . It has been documented that activated iNKT cells produce IL-4 more rapidly than most other cytokines (Wu and others 2009). Cytokines secreted by iNKT cells can also activate a variety of other cell types, including DCs, macrophages, NK cells, B cells, and conventional T cells (Van Kaer 2004; Parekh and others 2007). The studies presented here support the concept that $\gamma\delta$ -T cells and NK-T cells might be of significance in the control of immune responses and are affected by insults and sepsis (Wu and others 2009). This may be related to their ability to be activated nonspecifically by bacterial products or cytokines and to interact with components of the innate and adaptive immune responses and to regulate through direct cell-cell contact or by soluble mediators.

Regulatory B cells

In recent reports it was found that the secondary immunoparalysis state of septic shock is characterized by decreased T cells and B cells and proinflammatory cytokine release. The major cause of morbidity and mortality in patients with sepsis is immune suppression. Apoptosis of B cells is an important component in the loss of immune

competence in sepsis. B cells positively regulate immune response through antibody production and optimal $CD4^+$ T-cell activation. However, a specific and functionally important subset of B cells can also negatively modulate immune response through many of the known pathways, particularly in inflammation, autoimmunity, cancer, and infection (Bouaziz and others 2008). Regardless of this, many reports indicate that regulatory B-cell subsets modulate the function of T cells by presenting antigen, providing costimulation, and producing cytokines that direct the proliferation and effector functions of responding T cells. Distinct populations of cytokine-producing B cells can play opposite roles and can either enhance or suppress T-cell response (Lund and Randall 2010). For example, the production of cytokines, including IL-4, IL-6, IL-10, IFN- γ , and TGF- β is involved in immune regulation (Harris and others 2000; Tian and others 2001). In addition to promoting effector and memory $CD4^+$ T-cell response, B cells may also negatively modulate inflammation by generating Treg or NK-T-cell subsets, which can enhance $CD4^+CD25^+FoxP3^+$ Treg expansion in the central nervous system during experimental autoimmune encephalomyelitis, suppressing autoimmune inflammation (Tian and others 2001; Mann and others 2007; Beetz and others 2008; Gros and others 2008; Shah and Qiao 2008; Sun and others 2008b; Tu and others 2008; Chen and others 2009). Therefore, regulatory B cells play a pivotal role in the regulation of autoimmunity and inflammation that may also extend to tolerance regulation.

Important Molecules of Negative Immune Regulation in Acute Injuries and Sepsis

Sepsis is described as a complex clinical syndrome. It is a systemic inflammatory response to infection and results in a high morbidity and mortality. At the early phase of sepsis, lots of pro-inflammatory cytokines become amplified, whereas, at the late phase, inhibitory cytokines ensued, including IL-10 and TGF- β , which limit the strength of immune cell activation and expansion and negatively modulate inflammation. In addition, there are large amounts of immune molecules involved in negative immune regulation during sepsis, such as TNF- α induced protein 8 like-2 (TIPE2), heat shock protein (HSP), Zinc finger protein A20, and scavenger receptors.

The role of TIPE2 in negative regulation of immunity

Several facets of the interaction between host and pathogen must be considered in negative regulation in the process of acute injuries and sepsis, as we discuss in the following sections. A good example came from the research on TIPE2. TIPE2 shares considerable sequence homology with members of the TNF- α induced protein 8 (TNFAIP8) family, and preferentially expresses in lymphoid- and marrow-derived cells (Li and others 2009; Zhang and others 2009). It is essential for maintaining immune homeostasis, and it is highly expressed in inflammatory tissue but not normal tissue (Sun and others 2008a). Experimental evidence indicates that endogenous TIPE2 in LPS-stimulated macrophages can downregulate multiple signaling pathways. It was found that though TIPE2 might not be able to act on the extracellular signal-regulated kinase pathway, it inhibits the c-Jun N-terminal kinase (JNK) and p38, and thus, inhibits the

FIG. 1. Important molecules involved in negative immune regulation. The JNK, p38, and NF- κ B pathways were found to be regulated by the TIPE2 action. In addition to NF- κ B signaling pathways, the biological function of HSP-specific regulatory T cells can recognize induced HSP as presented by stress cells at the site of inflammation by production of suppressive cytokines such as IL-10. Zinc finger protein A20 is found to belong to a subfamily of 14 deubiquitination enzymes, which is also involved in negative regulation associated with TLR ligation. JNK, c-Jun N-terminal kinase; I- κ B, inhibitor of κ B; NF- κ B, nuclear factor- κ B; TNF- α , tumor necrosis factor- α ; TIPE2, TNF- α induced protein 8 like-2; HSP, heat shock protein; IL-10, interleukin 10; TLR, toll-like receptor; MAPK, mitogen activated protein kinase.

Immune Negative Regulation

activation of activator protein (AP)-1; TIPE2 exhaustion may enhance nuclear factor (NF)- κ B nuclear translocation and inhibitor of κ B (I- κ B) phosphorylation (Fig. 1). Sun and others (2008a) demonstrated that TIPE2 appeared to be a novel caspase-8-binding protein, which could regulate NF- κ B activation modulated by promoting Fas-induced apoptosis. There is evidence indicating that TIPE2 can inhibit activation of AP-1 and NF- κ B, and moreover, it is an essential negative regulator of toll-like receptor (TLR) and TCR signal activation (Sun and others 2008a; Li and others 2009; Zhang and others 2009). Further, experimental data have shown that LPS-induced sepsis in mice that were injected with a low dose of LPS, septic shock was dramatically accelerated and exacerbated in TIPE2^{-/-} mice compared with wild-type controls (Li and others 2009). Downregulation of TIPE2 expression resulted in elevated expression of Fas and increase in apoptosis of lymphocytes in patients suffering from systemic lupus erythematosus, and a deficiency in expression of TIPE2 could give rise to an elevation of serum levels of inflammatory cytokines, which are also important in inducing a procoagulant effect in sepsis, such as IL-1, IL-6, IL-12, and TNF- α (Li and others 2009). In addition, we have demonstrated that the expression of TIPE2 in normal BALB/C mouse CD4⁺CD25⁺ Tregs by Western blot and reverse transcription-polymerase chain reaction, and a decreased expression of TIPE2 gene markedly downregulated IL-10 and TGF- β levels, suggesting the potential effects of TIPE2 on Treg-mediated immune suppressive function in sepsis (Luan and others 2011). Although there are extensive studies regarding the potential role of TIPE2 in humoral and cellular immune responses, its multifarious function is still not fully

elucidated. According to a report, TIPE2 processed the function of regulating cell death (Sun and others 2008a). The data convincingly revealed that TIPE2 was able to bind caspase 8, but it was not found in the death-inducing signaling complex after Fas ligation and did not impair Fas-associated protein with death domain and caspase-8 recruitment (Chaudhary and others 1999; Bidere and others 2006; Takahashi and others 2006; Lemmers and others 2007; Freundt and others 2008; Sun and others 2008a; Zhang and others 2011). TIPE2 expression is upregulated in a variety of acute and chronic diseases including sepsis, and plays a key role in both the adaptive and innate immune systems, manifesting a negative regulatory effect in the maintenance of immune homeostasis (Freundt and others 2008; Zhang and others 2009; Xi and others 2011).

The biological function of HSP and its role in negative immunomodulation

HSP is a group of ubiquitous proteins within eukaryotic cells, and it is a large family. On the basis of their molecular weights, HSP can be stratified as HSP100, HSP90, HSP70, HSP60, HSP40, and the small HSP (Fink 1999). According to their individual function and mode of regulation, HSP can be divided into inducible HSP and constitutive HSP (Fink 1999). Under normal physiological and metabolic conditions, expression of HSP family members is mainly constitutive; however, when HSP is exposed to various forms of stress, such as hyperthermia, nutritional insufficiency, oxidative- and toxic-stress and inflammatory mediators, leading to a series of pathophysiological derangements, protein

FIG. 2. The impact of a negative regulator on pathogenesis and the development of sepsis, secondary to acute insults. Sepsis is a condition that results from a harmful or damaging host response to infection. The principal mechanism is that LPS is sensed via an LBP–LPS complex and then signaled through the TLR4–MD2 complex. NF- κ B plays a central role in regulating the transcription of cytokines, adhesion molecules, and other mediators involved in sepsis. Recently, it has been proposed that anti-inflammatory effect of lots of important regulators during anti-bacterial response resulted from suppression of T-cell proliferation and pro-inflammatory cytokine production most likely due to inhibition of NF- κ B/p50 transcription and subsequent reduction of NF- κ B activity. These include TIPE2, A20, HSP, CD163, and so on. LPS, lipopolysaccharide; LBP, LPS-binding protein; AP-1, activator protein-1; MD2, myeloid differential protein 2; MyD88, Myeloid differential factor 88; IRAK, interleukin receptor associated kinase; HIF-1 α , hypoxia inducible factor-1 α ; TRAF, TNF receptor associated factor.

expression of inducible HSP family members is increased (Lindquist and Craig 1988; Ellis 1990). These results demonstrate that HSPs play important roles of immune negative regulation. Many inducers of the heat shock response are known to block directly not only by stable I- κ B α activity but also by upregulation of its gene expression (Malhotra and Wong 2002; Wieten and others 2007). In the presence of inflammation, HSP-specific Tregs have been found to identify the expression of inducible HSP by blocking the anti-inflammatory cytokines (Fig. 2). Recently, McConnell and others (2011) found that HSP70 was a key determinant of mortality in aged, but not in young hosts with sepsis, which played a protective role in an age-dependent response to sepsis by preventing excessive gut apoptosis and both pulmonary and systemic inflammation. These findings support the view that HSP is critically involved in the process of negative regulation in the immune system and maintains immune homeostasis during sepsis.

Zinc finger protein A20 and the negative feedback regulation of the immune system

Zinc finger protein A20, which is also known as TNF- α induced protein-3 (TNFAIP3), inhibits NF- κ B activation via TNF receptor-associated factor pathway and is involved in negative feedback regulation (Sun 2008). Overexpression of zinc finger protein A20, TNF- α , IL-1, and LPS may block activation of NF- κ B and also can inhibit the production of TNF- α -mediated NF- κ B-dependent proteins, including E-selectin, vascular cell adhesion molecule-1, I- κ B α , IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (Boone and others 2004). It is reported that zinc finger protein A20 deficient mice produce larger amount of TNF- α , IL-

6, and nitric oxide than wild-type mice when challenged by LPS. Likewise, an *in vivo* study revealed that zinc finger protein A20 induced by LPS could protect mice from endotoxic shock by downregulating LPS-associated innate immunity (Boone and others 2004). The effect of LPS is a key component of the inflammatory response seen in Gram-negative sepsis. Zinc finger protein A20 is found to belong to a subfamily of 14-deubiquitination enzymes, which is involved in negative regulation associated with TLR ligation (Fig. 2). On the other hand, zinc finger protein A20 mediates its inhibitory function by downregulating key pro-inflammatory signaling pathways, including those controlling NF- κ B- and IRF3-dependent gene expressions (Boone and others 2004; Verstrepen and others 2010). Activation of these transcription factors is controlled by both K48- and K63-polyubiquitination of upstream signaling proteins, respectively triggering proteasome-mediated degradation or interaction with other signaling protein (Verstrepen and others 2010). Taken together, it could be demonstrated that zinc finger protein A20 plays an important role in cell-mediated immunity and also functions as an anti-inflammatory and antioxidant agent (Prasad 2007).

Scavenger receptors and immune negative regulation

Scavenger receptors are integral membrane proteins that bind a wide variety of ligands including modified or oxidized low-density lipoproteins, apoptotic cells, and pathogens, which are a large family with at least 8 different subclasses (A–H) that bear little sequence homology to each other, but could be recognized by common ligands (Droste and others 1999; Davis and Zarev 2005; Murphy and others

2005; Pluddemann and others 2007). They are expressed by myeloid cells, selected endothelial cells, and some epithelial cells, and they recognize many different ligands, including microbial pathogens and endogenous and modified host-derived molecules (Davis and Zarev 2005). CD163 was recently recognized as a member of the scavenger receptor cysteine-rich group B (SRCR-B) family, and it functions as a scavenger receptor for hemoglobin-haptoglobin complexes (Polfliet and others 2006) that is involved in cytoprotection and inflammation in both physiological and pathophysiological processes. Nevertheless, when abolished in large amounts, it can become toxic by mediating oxidative stress and inflammation. Therefore, CD163 plays a critical role in the control of inflammatory response, probably in part through its effect on both ferritin formation and subsequent induction of anti-inflammatory pathways through IL-10 and heme-oxygenase (Polfliet and others 2006). Another very important function of CD163 is the clearance of hemoglobin in its cell-free form and its participation in anti-inflammation in its soluble form, exhibiting cytokine-like functions (Onofre and others 2009). It is quite possible that scavenger receptor appears to be involved in negative immunomodulation after an acute insult, and it is used as a biomarker in different diseases and as a valuable diagnostic parameter for prognosis of many diseases, especially inflammatory disorders and sepsis, while the precise underlying mechanisms remain to be further elucidated.

The Role of Signaling Pathways in the Negative Immunomodulation of Acute Insults and Sepsis

Suppressor of cytokine signaling

In the settings of insults, shock, and sepsis, there exists the negative regulation of immunological function, which is essential for the regulation of signaling transduction, including the activation of signal transducer and activator of transcription (STAT) and suppressor of cytokine signaling (SOCS). First, increasing evidence supports that SOCS1, SOCS3, and SOCS5 play roles in coordinating Th1/Th2 cellular profiles. Consistent with these observations, T-cell-specific deletion of SOCS1 and SOCS3 results in enhanced production of both IFN- γ and IL-4 and differentiation into Th1 and Th2 cells, and negatively regulating IL-23 signaling pathway, leading to enhanced Th17 polarization, respectively (Fujimoto and others 2002; Chen and others 2006). Second, several distinct mechanisms have been described to mediate the pathway of Janus kinase (JAK)/STAT, however, the expression of SOCS proteins serves especially as an endogenous inhibitor involved in the JAK/STAT signaling pathway. There is increasing evidence that SOCS family proteins are inducible inhibitors of cytokine signaling, which are presented by several structurally related proteins and characterized by a central SH2 domain flanked by an N-terminal domain of variable length and a C-terminal SOCS box, including SOCS1-7 and SH2 domain-containing proteins (CIS) induced by cytokines. It should be noted that SOCS1, SOCS2, SOCS3, and CIS play critical roles in the process of negative immune regulation. Three groups of distinct approaches were discovered to search for proteins capable of inhibiting cytokine responses (Starr and others 1997), interacting with JAKs (Endo and others 1997; Onofre

and others 2009), and sharing homology with STAT SH2 domains (Naka and others 1997). Much of our understanding of SOCS function is derived from studies of SOCS1 and SOCS3. Both of them can block signaling by direct inhibition of JAK enzymatic activity, yet apparently it requires different anchoring points within the receptor complex. The SOCS1- and SOCS3-SH2 domain was shown to interact with Y1007 and JAK (Croker and others 2008). When CIS and SOCS2 bind receptor phosphotyrosines, they could inhibit signaling by competing with STAT recruitment receptor complex (Hotchkiss and Karl 2003). Nonetheless, whether other negative regulatory pathways failed to act upon the JAK/STAT pathway, inappropriate regulation of oncogene expression, or perturbed oncogene function remain unknown. Therefore, it is important to understand how SOCS is induced, what is the mechanism of JAK/STAT in the inhibition of SOCS proteins, and to clarify the potential role of SOCS proteins in the inhibition of JAK/STAT during sepsis (Hotchkiss and Karl 2003).

Negative regulation of TLR-mediated immune response

Advances in our understanding of cell-signaling pathways that mediate the response to microbes have demonstrated that the concept of blocking endotoxin to prevent septic complications may be simplistic (Wang and others 2009). However, there is still no efficient causal therapy applicable to patients. The importance of TLR for immune response against sepsis was demonstrated in humans exhibiting polymorphisms in TLR genes and in animal models using genetically modified mouse strains. TLRs are primary sensors of invading pathogens recognizing conserved microbial molecules and activating signaling pathways that are pivotal to innate and adaptive immune responses (Wang and others 2009). A TLR signaling pathway must be tightly controlled because its excessive activation can contribute to the pathogenesis of many human diseases (Chuang and Ulevitch 2004; Sibia 2004; Andrade and others 2005; Blanco and others 2005; Wang and others 2009), which might indirectly or indirectly regulate the immunosuppressive function in host response, in terms of immune negative regulation through different levels of modulation.

Under normal condition, degradation or destabilization of signal transduction factors is one of the critical mechanisms that reduces or terminates the activation of signaling pathways. In this regard, TLR signaling pathways have been known to be regulated by ubiquitin molecules via some negative regulators. Triad domain-containing protein 3 (Triad3) is one of the ubiquitin-modifying enzymes, acting as an E3 ubiquitin-protein ligase enhances ubiquitination and proteolytic degradation of certain TLRs (Andrade and others 2005). It has been found that overexpression of Triad3A may not affect TLR2 expression but promote substantial degradation of TLR4 and TLR9, and a decreased induction of TLR4 or TLR9 signaling may not affect TLR2 signaling (Schaaf and others 2009). TLR4, together with CD14 and the myeloid differential protein 2 (MD2) adapter molecule, serves as the main receptor for components from Gram-negative bacteria such as LPS, whereas TLR2 is crucial to the propagation of the inflammatory response to components from Gram-positive organisms, yeast and mycobacteria (Divanovic and others 2005). Moreover, it should be noted

that the ubiquitin-proteasome pathway is not the only negative regulator. There is growing evidence demonstrating that Tripartite-motif protein (Trim) 30 α is also a negative regulator of TLR in mediating NF- κ B, and it may target TAB2 and TAB3 for degradation. TLRs discriminated among different pathogen-associated molecules and activated signaling cascades that lead to immune response. Radio-protective105 expression is a specific homolog of TLR4; together with its helper molecule, MD1, it has a comforted association with TLR4/MD2, and this association inhibits LPS-TLR4/MD2 complex formation (An and others 2008). Indeed, TLR signaling pathways are involved in negative regulation by means of competing with the various adapters and transcription factors for binding sites (Wang and others 2009). Myeloid differential factor (MyD) 88 is an essential factor located in all TLRs except TLR3, which is composed of 3 main domains, namely the N-terminal death domain, the intermediate domain, and the TIR domain. Overexpression of MyD88 can inhibit LPS-induced NF- κ B activation (Naka and others 1997). However, MyD88s were not able to interact with IL-1 receptor-associated kinase-4, resulting in inhibition of the phosphorylation of IL-1 receptor-associated kinase-1 and the subsequent signaling transduction (van and others 1998). Therefore, it has become evident that disorder in functions of immune cells is closely related to signal transducing signal pathway induced by TLRs. The expression and function of TLRs are critical in the development of negative regulation of the innate immunity, and the regulation function plays a pivotal role in the control of the innate immunity during acute insults and sepsis.

Conclusions

In the setting of normal immune response or without acute injury from the environment, a balanced state between positive and negative regulations will be kept, and normal operation of vital movement will be maintained. However, excessive inflammatory reaction may be produced by trauma/burns, shock, and sepsis, and on top of it there will also be severe disorder in cell-mediated immunity, and all of them are closely related with negative regulation. The molecular mechanisms through which negative immune regulation is maintained are not fully understood, but recent studies imply that multiple molecules are involved (Fig. 2), and these molecules exert limiting effect on the intensity of immune cell activation and expansion. They include inhibitory cytokines (eg, TGF- β , IL-10, etc.), negative regulators of the antigen receptor and TLR signaling (eg, CTLA-4, I- κ B, SOCS1, and itch), and repressive transcription factors such as Foxp3 (Ranges and others 1987; Yamagiwa and others 2001; Zheng and others 2002; Rao and others 2005). As a conclusion it could be summarized that it is important to understand the exact role and mechanism of negative regulation of immune function in acute insults, shock, and sepsis, to adopt different methods of targeted intervention that will help restore the body's immune response, to prevent the occurrence and development of severe septic complications, and to provide new clues and ways for the prevention and treatment of severe sepsis.

Acknowledgments

This work was supported, in part, by grants from the National Natural Science Foundation (Nos. 30971192,

81130035, 81071545, 81121004) and the National Basic Research Program of China (No. 2012CB518102).

Author Disclosure Statement

No competing financial interests exist.

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Received November 24, 2011/Accepted January 16, 2012