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Review Article

Immunosuppression Following Surgical and Traumatic Injury

FUMIO KIMURA, HIROAKI SHIMIZU, HIROYUKI YOSHIDOME, MASAYUKI OHTSUKA, and MASARU MIYAZAKI

Department of General Surgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

Abstract
Severe sepsis and organ failure are still the major causes of postoperative morbidity and mortality after major hepatobiliary pancreatic surgery. Despite recent progress in understanding the immune conditions of abdominal sepsis, the postoperative incidence of septic complications after major visceral surgery remains high. This review focuses on the clinical and immunological parameters that determine the risk of the development and lethal outcome of postoperative septic complication following major surgery and trauma. A review of the literature indicates that surgical and traumatic injury profoundly affects the innate and adaptive immune responses, and that a marked suppression in cell-mediated immunity following an excessive inflammatory response appears to be responsible for the increased susceptibility to subsequent sepsis. The innate and adaptive immune responses are initiated and modulated by pathogen-associated molecular-pattern molecules and by damage-associated molecular-pattern molecules through the pattern-recognition receptors. Suppression of cell-mediated immunity may be caused by multifaceted cytokine/inhibitor profiles in the circulation and other compartments of the host, excessive activation and dysregulated recruitment of polymorphonuclear neutrophils, induction of alternatively activated or regulatory macrophages that have anti-inflammatory properties, a shift in the T-helper (Th)1/Th2 balance toward Th2, appearance of regulatory T cells, which are potent suppressors of the innate and adaptive immune system, and lymphocyte apoptosis in patients with sepsis. Recent basic and clinical studies have elucidated the functional effects of surgical and traumatic injury on the immune system. The research studies of interest may in future aid in the selection of appropriate therapeutic protocols.

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Key words Surgery · Trauma · Sepsis · Organ failure · Pattern-recognition receptors · Polymorphonuclear neutrophils · Monocytes/macrophages · T lymphocytes

Introduction

Severe sepsis is still a major cause of postoperative morbidity and mortality after major abdominal surgery. In particular, aggressive hepatobiliary pancreatic surgery, including an extended liver resection and radical pancreaticoduodectomy, has been associated with high complication rates of 40%–50%.[1–4] The most common complications following major hepatobiliary pancreatic surgery are septic complications, including cholangitis, wound infection, pneumonia, intra-abdominal abscess, fistula, and septicemia.[1–4] A recent clinical trial has reported that although organ-preserving pancreatic surgery potentially decreased the incidence of postoperative delayed gastric emptying in comparison with a pancreatoduodenectomy, there were no significant differences between the two groups in the incidence of pancreatic fistulas or other complications.[5] Despite recent progress in understanding the immune conditions of abdominal sepsis, the postoperative incidence of septic complications after major visceral surgery remains high.[1–4]

During the past decade, a number of experimental and clinical studies have provided evidence that surgical and trauma injury markedly affects the immune system, including both the specific and the nonspecific immune responses.[6–9] The protective immunity of the hosts may critically depend on an appropriate cytokine balance, a proper activation and recruitment of polymorphonuclear neutrophils (PMNs) and monocytes/macrophages, an intact macrophage–T-cell interaction, and an adequate T-helper (Th)1/Th2 conception of T-helper cell activation. The surgical and trauma injury potentially

disintegrates these complex regulatory systems and induces the deterioration of immune function.[6–9]

This review focuses on the clinical and immunologic parameters that determine the risk of the development and lethal outcome of postoperative septic complication following major surgery and trauma. The elucidation of these mechanisms is a prerequisite subject for the introduction of preventive and therapeutic strategies into clinical practice.

SIRS, CARS, and MODS

Major injury due to surgical or major trauma produces potentially profound immunological dysfunction resulting in tissue injury, postoperative infection, and multiple organ dysfunction syndrome (MODS) (Fig. 1). The immune system consists of an early innate and a late adaptive response. The initial proinflammatory immune response, or systemic inflammatory response syndrome (SIRS), is mediated primarily by the cells of the innate immune system. This is followed by a compensatory anti-inflammatory response syndrome (CARS) that is primarily mediated by cells of the adaptive immune system.[6–10]

Moore and Moore have described a model of early and late MODS depending on the initial degree of injury severity.[11] An initial massive traumatic insult can create an early vigorous proinflammatory response and severe SIRS independent of infection ("one-hit" model), resulting in early MODS. In the "two-hit" scenario, initially less severely-injured patients eventually develop late MODS as a result of the reactivation of their inflammatory response caused by an adverse and often minor intercurrent event, such as additional surgical stress, bacterial infections, or ischemia/reperfusion injury. Late MODS is often accompanied by CARS.[12] An unbalanced systemic compensatory anti-inflammatory response can result in anergy and immunosuppression, which predisposes the host to the development of opportunistic infection.

Cytokines, chemokines, stress hormones, and many other humoral mediators have been implicated in the pathogenesis of SIRS, CARS, and MODS in patients with severe surgical or traumatic injuries.[13,14] In response to major tissue injury and/or bacterial infection, endothelial and epithelial cells, as well as neutrophils, macrophages, and lymphocytes, produce powerful proinflammatory cytokines, especially tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6.[13] Polymorphonuclear neutrophils and macrophages respond to many of these mediators by releasing granular enzymes and producing reactive oxygen species (ROS) that ultimately lead to organ dysfunction.[14]

Chemokines have the ability to favor neutrophil and monocyte recruitment to the inflammatory site and to stimulate their subsequent activation.[15] According to the alignment of the sequences, chemokines can be classified into two families, one with the first two cysteines separated by one residue (CXC chemokines) and the other with the first two cysteines adjacent (CC chemokines). The CXC chemokines are neutrophil chemoattractants and include IL-8 and growth-related oncogenes in humans.[15] The CC chemokines are predominantly monocyte chemoattractants, and include macrophage chemoattractant protein (MCP)-1 and macrophage

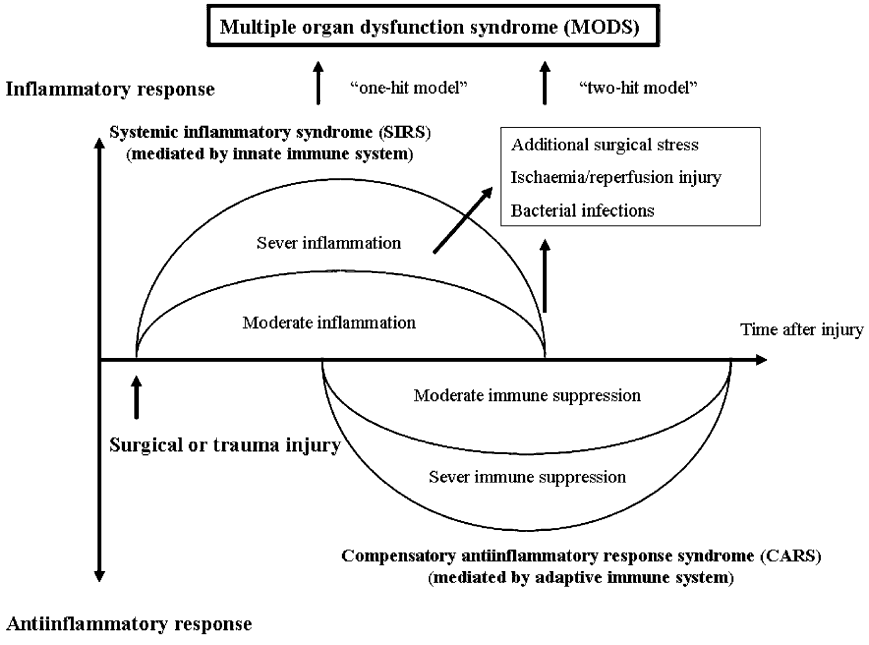

Fig. 1. A model of injury for systemic inflammatory response syndrome (*SIRS*), compensatory anti-inflammatory response syndrome (*CARS*), and multiple organ dysfunction syndrome (*MODS*). An initial massive insult can create an early vigorous proinflammatory response and severe SIRS independent of infection (one-hit model), resulting in early MODS. In the "two-hit" scenario, initially less severely-injured patients eventually develop late MODS as a result of the reactivation of their inflammatory response caused by additional surgical stress, ischemia/reperfusion injury, or bacterial infections. Patients surviving the early proinflammatory SIRS response to major injury may develop a counterinflammatory CARS response, which is associated with postoperative infection. Adapted from Ni Choileain and Redmond[7] and Moore and Moore[11]

inflammatory protein (MIP)-1α.[15] The postoperative serum levels of IL-8 and MCP-1 have been reported to correlate with surgical insult in patients who have undergone cardiovascular surgery.[16] Anti-inflammatory cytokines potentially suppress various innate immune functions and thereby render patients susceptible to postoperative infection.[17,18] In mouse models the rapid release of endogenous IL-10 has been reported to be an essential anti-inflammatory response controlling cytokine production during both Gram-negative and Gram-positive infection.[19,20] However, excessive production of IL-10 renders patients susceptible to infection. High serum IL-10 levels have also been reported to be associated with fatalities among patients with infection.[17] Interleukin-10 may also be involved in immune depression associated with hemorrhage.[21] Interleukin-4 also inhibits monocyte/macrophage function, including the ability to suppress monocyte-generated cytokines.[22]

Stress hormones may participate in the pathogenesis of postinjury infection and organ dysfunction.[23] Although activation of the hypothalamic-pituitary-adrenal axis is essential for response to severe stress,[24] excessive glucocorticoids may delay wound healing by promoting catabolism and inhibiting the immune system, leading to postoperative immunosuppression and infection.[25] Macrophage migration inhibitory factor (MIF), which is a proinflammatory pituitary and macrophage cytokine and a contraregulator of endogenous glucocorticoids, plays a critical part in the pathogenesis of septic shock.[26] Leptin, an adipocyte-derived hormone that acts centrally in hypothalamus to regulate body weight and peripheral energy expenditure, thereby helps to regulate the immune response.[27,28]

In humans, IL-6, IL-10, IL-8, MCP-1, cortisol, and leptin have been reported to be released after a liver resection in response to surgical stress, and are correlated with postoperative infection and organ dysfunction.[29] Cytokine antagonists also appear in the circulation, and the soluble TNF receptor p55 correlates with postoperative infection following surgery.[30] In these studies, increased plasma concentrations of proinflammatory and anti-inflammatory mediators were observed immediately after surgery or on postoperative day 1. These elevations occurred simultaneously for both the pro- and anti-inflammatory mediators. Similar circulating cytokine/inhibitor profiles have been observed in a mouse model of sepsis.[31] This multifaceted response questions the use of a simple proinflammatory cytokine measurement for classifying the inflammatory status of the patients with septic complications.[31] In addition, plasma levels should be carefully interpreted because they do not necessarily reflect the immune status in other compartments of the host. Nevertheless, due to a lack of more clinically useful markers, determination of pro- and anti-inflammatory cytokine levels in plasma has become more and more important in the intensive care unit when dealing with surgical patients.[6]

Toll-Like Receptors, Nucleotide-Binding Oligomerization Domain-Like Receptors, and Purinergic Receptors

The pattern-recognition receptors (PRRs) play a central role in the initiation of the innate and adaptive immune response to infection (Fig. 2). Membrane-bound or vesicular (endosomal) PRRs, including the Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and RIG-I-like receptors (RLRs) recognize microorganisms derived products, so-called pathogen-associated molecular-pattern molecules (PAMPs) and activate intracellular cascades.[32,33] Toll-like receptors sense the presence of PAMPs extracellularly and in phagosomes, whereas the cytosolic NLRs recognize PAMPs in intracellular compartments.[34] RIG-I-like receptors are cytoplasmic proteins that recognize viral RNA.[35]

Toll-Like Receptors

In humans, extracellular bacterial products are sensed by five TLRs. Lipopolysaccharide (LPS) is the main bacterial ligand for TLR4; lipotechoic acid and diacylated lipopeptides are sensed by a TLR2–TLR6 dimer; triacylated lipopeptides are sensed by a TLR2–TLR1 dimer; CpG motifs are sensed by TLR9, and flagellin is sensed by TLR5. For antifungal responses, a TLR2–TLR6 dimer senses zymosan. Five TLRs are involved in antiviral responses: TLR4 senses F protein from respiratory syncytial virus; double-stranded RNA is sensed by TLR3; TLR9 senses viral CpG DNA; and TLR7 and TLR8 sense single-stranded viral RNA. Protozoal products such as glycosylphosphatidylinositol-anchor proteins are also sensed by TLR2. Therefore, almost all pathogens that infect humans will be sensed by TLRs.[33] Toll-like receptor signaling potentially activates nuclear factor-κB (NF-κB) through myeloid differentiation primary-response protein 88 (MyD88). MyD88 is a TLR signaling adaptor protein that is used by all TLRs except TLR3. It interacts with the IL-1 receptor-associated kinase (IRAK) family, leading to interaction with tumor necrosis factor receptor-associated factor 6 (TRAF6), which ultimately leads to activation of NF-κB and mitogen-activated protein (MAP) kinases (Fig. 2). These pathways lead to the production of such cytokines as TNF and other proinflammatory proteins.[33]

In addition, monocytes and PMNs from patients with sepsis have been reported to exhibit significantly higher TLR-2 and TLR-4 expression levels than controls.[36] Furthermore, in severely injured patients, the carriage

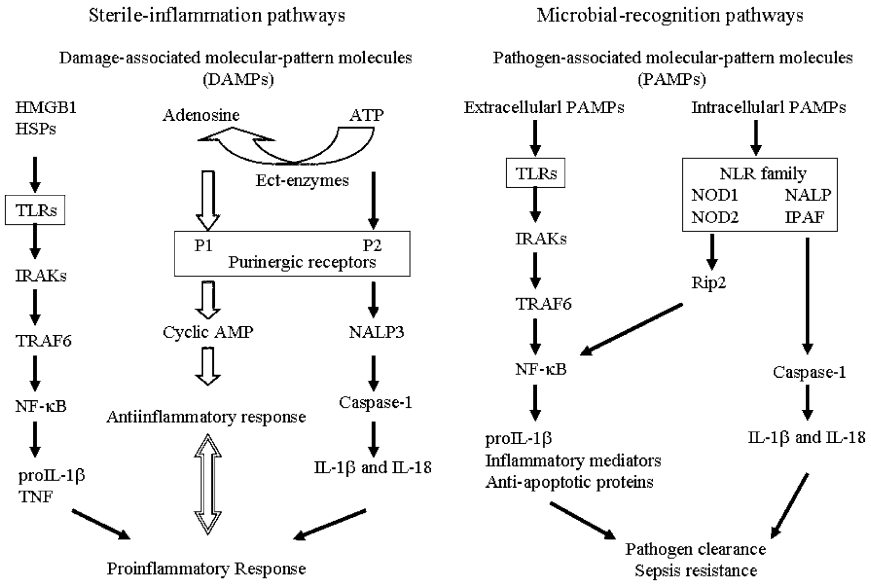

Fig. 2. Pathogen-associated molecular-pattern molecules (*PAMPs*) and damage-associated molecular-pattern molecules (*DAMPs*). Toll-like receptors (*TLRs*) sense the extracellular presence of so-called PAMPs, whereas nucleotide-binding oligomerization domain (*NOD*)-like receptors (*NLRs*) recognize PAMPs in intracellular compartments and activate intracellular cascades. NOD1, NOD2, NALP, and IPAF are included in NLR family. Extracellular adenosine triphosphate (*ATP*) potentially contributes to the onset of acute inflammation through P2 receptors. Conversely, extracellular adenosine, a metabolite of ATP, induces an anti-inflammatory response through P1 receptors. *HMGB1*, high-mobility group box 1; *HSPs*, heat shock proteins; *IRAK*, IL-1 receptor-associated kinase; *TRAF6*, tumor necrosis factor receptor-associated factor 6; *NF-κB*, nuclear factor κB; *Rip2*, receptor-interacting protein 2

of the variant TLR4 896 G allele has been reported to be associated with a decreased risk of complicated sepsis.[37]

Nucleotide-Binding Oligomerization Domain-Like Receptors

The NLR family is divided into subfamilies on the basis of their signal transduction domains (Table 1), and recent studies have highlighted the role of certain NLRs, including NOD1, NOD2, NALP, and IPAF in the detection of intracellular microbes.[38] NOD1 and NOD2 can detect muropeptides derived from peptidoglycan (PG). NOD2 detects muramyl dipeptide, a motif that is present in the PGs of both Gram-positive and Gram-negative bacteria, whereas the recognition of bacterial PG by NOD1 is dependent on the presence of the meso-DAP, an amino acid characteristic of most Gram-negative and some Gram-positive bacteria. Therefore, NOD1 is involved in the immune response to *Escherichia coli*, *Chlamydia pneumoniae*, *Campylobacter jejuni*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, and *Helicobacter pylori*, whereas NOD2 recognizes *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, and *Listeria monocytogenes*. The NOD proteins recruit the serine–threonine kinase Rip2, which in turn leads to NF-κB activation.[38] Other NLRs activate caspase-1, which results in the processing and release of the proinflammatory cytokines IL-1β and IL-18 (Fig. 2). In response to specific microbial or bacterial factors, the NLR proteins assemble a caspase-1-activating inflammasome complex. Several inflammasomes have been defined by the NLR protein that they contain: the NALP1 inflammasome, the NALP3 inflammasome, and the IPAF inflammasome[38–40] (Table 1). Gram-positive bacteria such as *L. monocytogenes*, *S. aureus*, and Gram-negative *Aeromonas hydrophila* activate NALP3 using pore-forming toxins. Activated NALP3 recruits apoptosis-associated speck-like protein (ASC) through a homophilic pyrin domain interaction. Apoptosis-associated speck-like protein in turn recruits procaspase-1 via homophilic caspase recruitment domain (CARD)–CARD interaction, which leads to activation of caspase-1, and active caspase-1 can then process pro-IL-1β and pro-IL-18.[39] IPAF recognizes flagellin secreted by Gram-negative pathogens, and can interact directly with the caspase-1 CARD domain.[40]

NOD2 leucine-rich repeat variants have been reported to be closely associated with susceptibility to Crohn's disease.[41] Recently, the monocyte expression of the inflammasome mRNAs for NALP1, ASC, and caspase-1 has been reported to be significantly lower in patients with septic shock compared with critically ill control subjects.[42] Furthermore, the NALP1 mRNA

Table 1. Domain structure of the human NOD-like receptor (NLR) family and the inflammasomes

NLR subfamily	Domain structure		Bacterial species sensed by NOD-like receptor
NOD	NOD1	CARD–NACHT–NAD–LRR	*Escherichia coli*, *Chlamydia pneumoniae* *Campylobacter jejuni*, *Salmonella typhimurium* *Pseudomonas aeruginosa* and *Helicobacter pylori*
	NOD2	CARD–CARD–NACHT–NAD–LRR	*Streptococcus pneumoniae*, *Mycobacterium tuberculosis, Listeria monocytogenes*
NALP3 inflammasome			
	NALP3	PYD–NACHT–NAD–LRR *	*Listeria monocytogenes*, *Staphylococcus aureus* *Aeromonas hydrophila*, microbial toxins
	ASC	CARD–PYD *	
	Caspase-1	CARD–CASPASE	
IPAF inflammasome			
	IPAF	CARD–NACHT–LRR *	*Salmonella typhimurium*, *Pseudomonas aeruginosa* *Legionella pneumophila*
	Caspase-1	CARD–CASPASE	

Adapted from Carneiro et al.,[38] Martinon,[39] and Sutterwala et al.[40]
The LRR domains of the NLRs can sense the activating signals. The core structure of the NALP inflammasome consists of a NALP, the adaptor ASC, and caspase-1. The NACHT–NAD region initiates oligomerization of NALP. PYD–PYD, and CARD–CARD homotypic interactions (*) are essential for the recruitment and activation of the adaptor ASC and the inflammatory caspases, respectively. IPAF can interact directly with the caspase-1 CARD domain
ASC, apoptosis-associated speck-like protein; CARD, caspase recruitment domain; IPAF, interleukin-1 converting enzyme (ICE) protease-activating factor; LRR, leucine-rich repeat; NACHT, domain present neuronal apoptosis inhibitory protein; NAD, NACHT-associated domain; NALP, NACHT, LRR, and PYD containing proteins; PYD, Pyrin domain

levels are linked to survival in patients with sepsis, thus suggesting that the NALP1 inflammasome plays a critical role in the pathogenesis of sepsis in humans. However, in that study, the monocyte expression of NOD1 and NOD2 is not affected by sepsis.

Damage-Associated Molecular-Pattern Molecules

Pattern-recognition receptors can recognize some endogenous ligands released from damaged tissues and activate immune response of the host (Fig. 2). These endogenous ligands released by damaged or dying cells have been termed damage-associated molecular-pattern molecules (DAMPs) because they contribute to the induction of inflammation through PRRs.[43] DAMPs include the chromatin-associated protein high-mobility group box 1 (HMGB1), heat shock proteins (HSPs), S100 proteins, products of purine metabolism (uric acid, adenosine triphosphate [ATP], and adenosine), and others.[44]

HMGB1, a typical DAMP, is a ubiquitous nuclear protein that binds to nucleosomes and promotes DNA bending. There are two ways in which HMGB1 can be released into the extracellular environment: active secretion from cells of the innate immune system or passive release from necrotic cells. Similar to proinflammatory cytokines, the active secretion of HMGB1 from monocytes or macrophages follows activation by microbial and proinflammatory stimuli.[44,45] In a standardized mouse model of endotoxemia, HMGB1 secreted by activated macrophages acts as a late mediator of inflammation. The serum HMGB1 levels begin to increase 12–18 h after TNF levels peak, which occurs at 2 h, and after IL-1 levels peak, which occurs at 4–6 h.[46] In addition, HMGB1 is passively released from cells undergoing nonprogrammed cell death, and initiates inflammation. In contrast, apoptotic cells modify their chromatin so that HMGB1 irreversibly binds and is therefore not released. HMGB1 has been reported to transduce cellular signals by interacting with at least three receptors: TLR4, TLR2, and the receptor of advanced glycation endproducts (RAGE).[44,45] It has been reported that HMGB1 acts as a mediator of inflammation and organ damage in experimental models of LPS-induced acute lung injury (ALI),[47] hemorrhage-induced ALI,[48] and hepatic ischemia reperfusion injury.[49] In humans, HMG1 may also be involved in the pathogenesis of sepsis,[50] hemorrhagic shock,[51] and sepsis-induced ALI.[52] However, no predictable correlation between serum levels of HMGB1 and severity of infection has been found in patients with sepsis.[53]

Heat shock proteins are stress-inducible proteins that protect against cellular injury as a molecular chaperone, playing an essential role in mediating protein folding, assembly, transport, and degradation. It has been docu-

mented that extracellular HSPs potentially act as an endogenous ligand for the CD14, TLR-4, and MD2 complex, which mediates the activation of NF-κB and the synthesis of proinflammatory cytokines.[54,55] Furthermore, it has been reported that circulating HSP70 plays a pivotal role in postoperative inflammatory response after open-heart surgery[56] and after liver resection.[57] Therefore, even in the absence of pathogens, disrupted or injured cells recruit innate inflammatory cells by releasing DAMPs.[43]

Purinergic Receptors

The purinergic receptors may also play an important role in regulation of immune response to tissue injury. The purinergic receptors determine the variety of effects induced by extracellular ATP and adenosine released from injured tissue.[58] Two families of purinergic receptors have been defined to date, namely the P1 and P2 receptors (Fig. 2). The P1 receptors are subdivided into the A1, A2A, A2B, and A3 receptor subtypes. Upon injury or infection, damaged tissue cells release intracellular ATP into their extracellular microenvironment. Extracellular ATP potentially contributes to the onset of acute inflammation through P2 receptors expressed by neutrophils and macrophages. The activation of the P2X7 receptor by ATP triggers the assembly of the NALP3 inflammasome, thus resulting in IL-1β secretion. Conversely, extracellular adenosine, a metabolite of ATP, contributes to alternative macrophage activation through P1 receptors and induces an anti-inflammatory response. The activation of the A2 receptor by adenosine leads to an increase in intracellular cyclic adenosine monophosphate (AMP), which inhibits the intracellular signaling of proinflammatory pathways in immune cells. Adenosine inhibits virtually all effector functions of neutrophils, macrophages, and T lymphocytes.[58] Most immune cells coexpress both P1 and P2 receptor subtypes, which suggests the dual regulation of cell function through purinergic signaling. Furthermore, external ATP is quickly converted to adenosine by ectoenzymes. Therefore, the nature of the effects induced by extracellular ATP and adenosine may shift from immunostimulatory to immunoregulatory, depending on the mechanisms that control ATP release, expression of the ectoenzymes, and the availability of the P2 and P1 receptors.[58]

A2 adenosine receptors have been reported to potentially be able to counteract collateral tissue damage due to excessive inflammation.[59] In the inflammatory tissue, activated immune cells might cause direct tissue damage. In addition, the increased expression of adhesion molecules might result in the augmented binding of neutrophils to the blood vessel walls, leading to vascular occlusions, local tissue hypoxia, and indirect collateral tissue damage. Tissue hypoxia is conducive to the accumulation of extracellular adenosine. Sufficiently high extracellular adenosine levels will trigger the maximal activation of high-affinity A2A and low-affinity A2B adenosine receptors, reducing excessive inflammation and collateral tissue damage.[59] It has also been reported that adenosine generation catalyzed by the ecto-apyrase (CD39) and 5′-nucleotidase (CD73) expressed on regulatory T cells (Tregs) mediates immune suppression.[60] CD39 degrades ATP and adenosine diphosphate (ADP) into adenosine monophosphates and CD73 catalyzes the conversion of AMP into adenosine. Therefore, CD39-mediated removal of the proinflammatory ATP and its conversion into immunosuppressive adenosine by CD73 represent an additional mechanism by which Tregs can suppress immune response.[61] The clinical significance of the purinergic receptors, however, remains to be investigated.

Polymorphonuclear Neutrophils

Polymorphonuclear neutrophils play a central role in the innate immune response as the archetypical phagocytic cells. PMNs actively seek out, ingest, and destroy pathogenic microorganisms by means of ROS, proteinases, and antimicrobial peptides.[62,63] Ordered recruitment and activation of PMNs requires the presence of chemoattractants and the leukocyte adhesion molecules of the integrin family. The β2 integrins (CD11/CD18) in particular are critically involved in firm adhesion and migration of PMNs.[62] It has been reported that CD11b (the adhesion/complement receptor) expression and ROS generation of PMNs are increased soon after surgical injury[64,65] and after traumatic injury.[66,67] The activation of PMNs is closely associated with visceral ischemia,[68] LPS absorption,[69] SIRS,[65] and postoperative sepsis.[66] Polymorphonuclear neutrophils are also activated for increased elastase release following major surgery or trauma.[70,71] Furthermore, spontaneous apoptosis of PMNs has been reported to be significantly delayed in patients who had undergone elective surgery.[67] These reports suggest that activation of PMNs is induced by surgical or trauma injury according to the severity of tissue damage, and is potentially accelerated by LPS and bacterial challenge. The activated functionality and prolonged survival of PMNs may represent an appropriate adaptive response to injury to eliminate invading pathogens. In contrast, the presence of activated and apoptosis-resistant PMNs may play a major role in the pathogenesis of ALI and acute respiratory distress syndrome (ARDS).[72,73] Moreover, the accumulation of primed PMNs into tissues, accompanied with systemic activation of complement and coagulation system, can lead to distant organ damage and MODS.[74,75]

Acute Lung Injury, Acute Respiratory Distress Syndrome, and Pneumonia

The two most important chemokines for PMN recruitment are IL-8/CXCL8 and growth-related oncogene α (GRO-α)/CXCL1. Growth-related oncogene α is present in greater concentration in the lung than IL-8 in patients with pneumonia and ARDS.[76–78] Furthermore, IL-8 binds to both CXCR1 and CXCR2, whereas GRO-α only binds to the CXCR2.[77] Therefore, GRO-α and CXCR2 can participate in the pathogenesis of ARDS and pneumonia in humans. In a mouse model of *Pseudomonas* pneumonia, the neutralization of CXCR2 results in a striking increase in mortality, which is associated with a marked decrease in neutrophil recruitment and bacterial clearance. Conversely, the site-specific transgenic expression of keratinocyte-derived chemokine (KC)/CXCL1 results in enhanced clearance of bacteria after *Pseudomonas* challenge.[79] It has been reported that in major trauma patients, CXCR2 responses are markedly diminished in the PMNs of patients who progress to sepsis and pneumonia, but are elevated in PMNs from patients who progress to ARDS.[80,81] These reports suggest that high CXCR2 activity may correlate with PMN priming and outcomes such as ALI and ARDS (Fig. 3), whereas the suppression of CXCR2 function in inflammatory environments may impair PMN recruitment to the lung and predispose patients to pneumonia and sepsis.

Polymorphonuclear Neutrophil Function in Sepsis

In the nonpulmonary organs, the augmented binding of PMNs to blood vessel walls might cause indirect tissue damage (Fig. 3). The activated PMNs adhere so strongly to the endothelium of postcapillary venules that they produce vascular occlusions, leading to tissue hypoxia and hypoperfusion. Alternatively, PMNs primed by circulating inflammatory factors bind tightly to the endothelium, and are readily activated by chemokines expressed on the endothelial surface in response to an underlying inflammatory or infective lesion. This untoward activation of PMNs results in the release of lytic factors that induce endothelial dysfunction, the opening of intercellular junctions, and increase vascular permeability.[82] Therefore, vascular occlusions and endothelial dysfunction due to activated PMNs might be the major causes of organ dysfunction in sepsis.

However, the role of the effector function of neutrophils in patients with sepsis has been poorly investigated. There are data showing that neutrophil adherence and transmigration are impaired in septic patients.[83] Although CXCR1 expression is maintained on neutrophils during severe sepsis, desensitization of G-protein-coupled receptors (GPCRs), caused by the steric hindrance of the receptors due to receptor phosphorylation by GPCRs kinases (GRK), might be one of the mechanisms for PMN dysfunction.[84,85] Endogenous mediators produced during sepsis might continually activate circulating neutrophils and induce GRK activation, leading to GPCR phosphorylation.[84] Desensitization of GPCRs, including CXCR1, may impair chemoattractant-induced tyrosine kinase activity and the subsequent rearrangement of the actin network, therefore compromising the ability of neutrophils from patients with sepsis to migrate.[84,85]

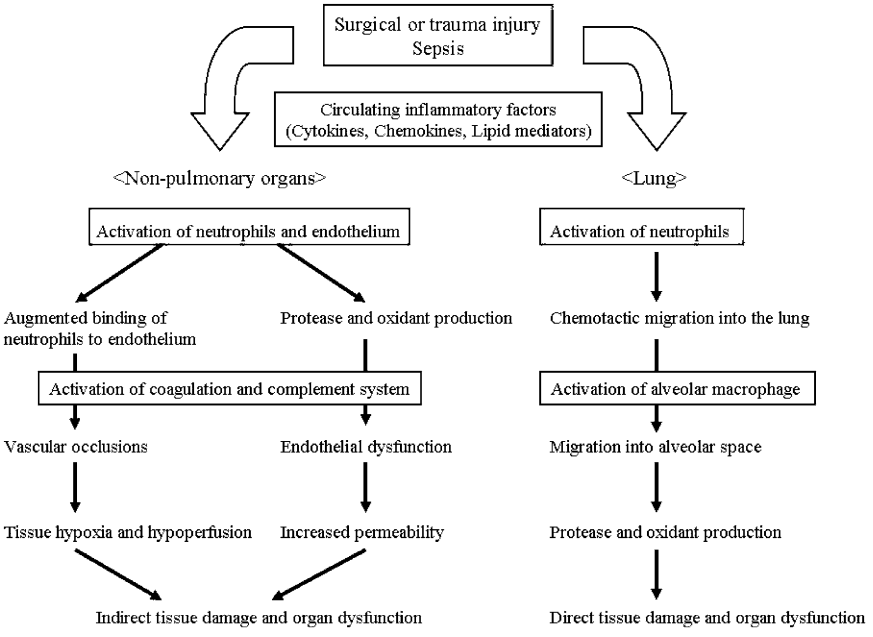

Fig. 3. Models of tissue damage and organ dysfunction in patients with major injury and sepsis. In nonpulmonary organs, vascular occlusions and endothelial dysfunction due to activated neutrophils and endothelium appear to be the major causes of organ dysfunction. Activation of the coagulation and complement system might also be involved in this process. In the lung, infiltrating neutrophils can induce direct damage resulting in acute lung injury and acute respiratory distress syndrome. Accumulation of neutrophils in the lung depends on the chemokines that are produced by alveolar macrophages. Suppression of chemokine functions may in turn impair neutrophil recruitment to the lung and predispose the lung to pneumonia and sepsis

Martins et al. reported that ROS generation and phagocytosis of PMNs are upregulated in patients with sepsis.[86] In contrast, Kaufmann et al. have reported that phagocytosis of zymosan and the associated ROS production are significantly decreased in patients with septic shock.[87] These reports suggest that the development of PMN dysfunction depends on sepsis severity. Danikas et al. evaluated the impact of the phagocytic activity of PMNs on the outcome of patients with severe sepsis, and have reported that a reduced phagocytic activity of PMNs during the first 24 h after admission is a negative predictor for survival and that phagocytic activity of PMNs is strongly correlated with the expression of CD64,[88] the high-affinity receptor for IgG1 and IgG3 expressed by mononuclear phagocytes and activated neutrophils.[89] It has been reported that the phagocytic capacity of immature neutrophils is lower than in mature neutrophils.[90] An increase in immature neutrophils in severe sepsis may therefore undermine the overall phagocytic efficacy of a host, despite the observed leukocytosis.

Monocytes/Macrophages

The mononuclear phagocyte system (MPS) displays a remarkable functional diversity, allowing cells to perform multiple defense functions from pathogen elimination by phagocytosis to the induction of antigen-specific T-cell responses. Therefore, MPS plays a central role in the innate immunity and orchestrates the adaptive immunity.[91,92]

Monocytes

Circulating blood monocytes supply peripheral tissues with macrophage and dendritic cell precursors and, in the setting of infection, also directly contribute to immune defense against microbial pathogens. In humans, circulating monocytes are divided into two subsets on the basis of the expression of CD14. CD14highCD16– monocytes, which consist of a majority of circulating monocytes and are often called "inflammatory monocytes," express high levels of CCR2, and traffic to sites of microbial infection in response to MCP-1/CCL2 secretion.[91,92] In contrast, CD14lowCD16+ monocytes, which are called "resident monocytes," express higher amounts of MHC class II molecules than CD14highCD16– monocytes, high levels of CXCR1, and low levels of CCR2. These cells have been suggested to resemble mature tissue macrophages such as splenic macrophages, Kupffer cells, alveolar macrophages, microglia, and osteoclasts.[91,92]

Macrophages

Macrophages are heterogeneous cells and have been broadly classified into two groups according to functional polarization: classically activated macrophages and alternatively activated macrophages.[93] However, recent experimental studies have shown that macrophage activation is plastic, rapid, and fully reversible in response to environmental cues, and that there might be at least three macrophage populations based on different physiological activities[92–94] (Table 2).

Classically activated macrophages arise in response to interferon-γ (IFN-γ), which can be produced during an adaptive immune response by Th1 cells or during an innate immune response by natural killer (NK) cells; and in response to TNF, which is produced by antigen-presenting cells. Classically activated macrophages have microbicidal activity, produce high levels of IL-12, modest levels of IL-10, and release reactive oxygen and nitrogen intermediates.[92–94] Wound-healing (alternatively activated) macrophages arise in response to IL-4, which can be produced during an adaptive immune response by Th2 cells or during an innate immune response by granulocytes. Wound-healing macrophages produce low levels of IL-12 and IL-10, and are involved in tissue repair.[92–94] The third macrophage population is

Table 2. Macrophage heterogeneity during inflammation

Populations of macrophages	Inducer	Function
Classically activated macrophages	IFN-γ (Th1, NK), TNF (APCs) LPS, microbial product	Microbicidal activity Production of proinflammatory cytokines, and ROS
Wound-healing macrophages (Alternatively activated)	IL-4, IL-13 (Th2)	Tissue repair Parasite killing
Regulatory macrophages	IL-10 (Tregs) Immune complexes, prostaglandins, GPCR ligands, glucocorticoids, apoptotic cells	Anti-inflammatory activity Production of IL-10, TGF-β, and prostaglandin E2

Adapted from Gordon and Taylor,[92] Benoit et al.,[93] and Mosser and Edwards[94]
IFN-γ, interferon-γ; Th, T helper; NK, natural killer; APCs, antigen-presenting cells; LPS, lipopolysaccharide; ROS, reactive oxygen species; Tregs, regulatory T cells; GPCR, G-protein-coupled receptor; TGF-β, transforming growth factor-β

regulatory macrophages, which are generated in response to various stimuli including immune complexes, prostaglandins, GPCR ligands, glucocorticoids, apoptotic cells, adenosine, or IL-10. Regulatory macrophages produce high levels of IL-10 and low levels of IL-12 to suppress immune responses.[92–95] Regulatory macrophages also produce transforming growth factor-β (TGF-β) and prostaglandin E2, and show reduced expression of MHC class II molecules. Following surgical or traumatic injury, these macrophage populations may be highly dynamic. Classically activated macrophages and regulatory macrophages can first take part in SIRS and CARS, respectively, and then wound-healing macrophages participate in the resolution of inflammation and tissue repair.[92–94]

Iinterleukin-12 and Human Leukocyte Antigen-DR Expression

In patients with infection following surgical, trauma, or burn injury, circulating monocytes show reduced production of IL-12[96,97] and suppressed expression of human leukocyte antigen (HLA)-DR.[98–101] Depressed IL-12-producing activity by monocytes correlates with an adverse clinical course in severely injured trauma patients.[96] Also, preoperative impaired monocyte IL-12 production has been observed in patients with the lethal outcome of postoperative sepsis.[97] Expression of HLA-DR on circulating blood monocytes has been shown to be depressed in patients following trauma,[98] major surgery,[99,100] and burn injury.[101] In these reports, the suppression of HLA-DR expression correlates with severity of infectious complication and poor outcome.[98–101] Furthermore, a reduction in HLA-DR expression rate is a sensitive indicator of poor outcome in cases of sepsis, severe sepsis, or septic shock.[102,103] These reports suggest that monocyte deactivation such as suppression of IL-12 production and HLA-DR expression is closely related to immuno-paralysis following major injury and in severe sepsis.

Interleukin-10 and Transforming Growth Factor-β

In patients with sepsis, a reduction of monocyte HLA-DR expression is inversely affected by serum IL-10 levels or IL-10 mRNA expression in peripheral leukocytes.[104–106] Interleukin-10 has been shown in vitro to potentially suppress the HLA-DR expression on human monocytes[107,108] and IL-12 production by human monocyte at the transcriptional level.[109] Moreover, circulating IL-10 levels are a remarkable predictor of postoperative infection and fatal outcome of sepsis.[106] Therefore, IL-10 plays a major role in the pathophysiological mechanism of monocyte deactivation following major injury and in sepsis. Transforming growth factor-β has also been described in vitro to play a role in monocyte deactivation.[110,111] However, the circulating TGF-β level is not observed to increase in patients with sepsis. It tends to either be lower in severe sepsis[105,112] or is not significantly different from controls.[103,113] Therefore, IL-10 is likely more important than TGF-β regarding the pathophysiology of monocyte deactivation following major injury and in severe sepsis.

Toll-Like Receptors

Toll-like receptor signaling might be another key factor in monocyte deactivation during severe sepsis. It has been reported that TLR-2 and -4 expression levels are significantly increased in monocytes from both septic and surgical patients.[114,115] Continuous microbial stimulation during bacterial sepsis with a number of different antigenic structures might result in cell activation, inducing receptor upregulation.[116] Causative factors may include the release of cytokines during sepsis, such as IL-6, which has been shown to upregulate TLR4 on human monocytes.[117] However, Tsujimoto et al. have reported that despite increased expression of TLRs, IL-1β production from LPS-stimulated peripheral blood mononuclear cells (PBMCs) is significantly reduced in patients with sepsis compared to surgical and control patients.[114] Recently, Salomao et al. have revealed that TLR signaling gene expression in mononuclear cells is dynamically modulated across the stages of sepsis, and is decreased in more severe forms of the disease. In contrast, broad gene upregulation is present throughout the stages of the disease in PMNs.[118]

Phagocytosis and Reactive Oxygen Species Generation

The phagocytic function and ROS generation of monocytes in sepsis has been poorly investigated. It has been reported that increased phagocytic function of monocytes, as estimated by expression of CD64 antigen, was favorably correlated to patient survival.[88] Reactive oxygen species generation is upregulated in monocytes from septic patients and it is differentially modulated depending on the stage of the disease and the stimuli.[119] Moreover, ROS generation of monocytes significantly correlates with sepsis-associated organ failure assessment score in patients with severe sepsis and septic shock.[119] These reports suggest that early in the disease process, increased phagocytic function and a vigorous ROS generation may be desirable and important to restrain the infecting microorganisms, and that later in this process the persistence of increased ROS generation may be deleterious, promoting sepsis-associated organ failure. This upregulated ROS generation of monocytes contrasts with monocytes dysfunction such as the downregulation of cytokine production and

HLA-DR expression. It has been reported that antimicrobial peptides such as defensins α and LPS amplify ROS release in a TLR4-independent manner, possibly by exerting a prolonged catalytic effect on the ROS generating enzymes, whereas antimicrobial peptides inhibit cytokine and nitric oxide (NO) induction by LPS in a TLR4-dependent manner.[120]

Nitric Oxide

Nitric oxide has well-known vasodilatory effects in sepsis, and has pro- and anti-inflammatory and oxidant and antioxidant properties.[121] Previous experimental studies support a role for inducible NO synthase (iNOS) in the pathogenesis of severe sepsis.[121] The vasodilatory effect of NO is clearly involved in the development of hypotension during septic shock. Nevertheless, NOS inhibition in animal models and septic shock patients could not improve and even aggravated the patient outcome, suggesting a bivalent role for NO. Although excessive NO production provokes lethal hypotension, it also has an important antioxidant function, protecting organs from oxidative stress and lipid peroxidation.[122] It has been accepted that macrophages and other hematopoietic cells such as PMNs are the principal source of high systemic NO levels during septic shock. However, it has been shown that a wide range of nonhematopoietic cells such as hepatocytes, epithelial, vascular smooth muscle, and endothelial cells have the ability to express iNOS in response to LPS or cytokines in rodents.[123]

In humans, there is far less evidence for increased NOS induction during sepsis. Plasma nitrite/nitrate concentrations increase during sepsis, and inversely correlate with mean arterial pressure and systemic vascular resistance.[124] Serum nitrite/nitrate concentrations are also increased in patients with postoperative sepsis.[125] The increased serum nitrite/nitrate levels that are found during postoperative sepsis correlate with the severity of the septic course.[126] Therefore, iNOS and NO might play a role in the pathophysiology of patients with sepsis or septic shock. The cell sources of NO in human sepsis remain unclear. In patients with ARDS following sepsis, significant expression of iNOS has been shown in alveolar macrophages, and nitrites/nitrates are elevated in the supernatant of bronchoalveolar lavage fluid.[127] The frequency of iNOS expression in PMNs is observed to increase in sepsis and SIRS patients compared to non-SIRS patients.[128] These reports suggest that macrophages and PMNs are the principal source of NO during sepsis. However, it has been reported that although human mononuclear phagocytes can produce iNOS mRNA and protein in vitro, their abilities to generate NO are very low.[129] In patients with septic shock, iNOS activity is increased in putrescent areas, but is compartmentalized at the very site of infection.[124] These reports suggest that in humans, NO synthesis is more restricted than in other species.

Lymphocytes

Early studies have reported that the mitogenic response of circulating lymphocytes to the T-cell mitogen phytohemagglutinin and/or concanavalin A is potentially altered by major surgery, multiple trauma, and thermal injury.[130–133] In these reports, the degree of lymphocyte suppression correlates with the complexity of surgery[130] or severity of injury.[133] In addition, the degree of lymphocyte suppression correlates with the subsequent development of infectious complications and mortality.[131–133] These reports suggest that major surgical injury can lead to depression of the mitogenic response of lymphocytes, resulting in subsequent development of infectious complications.

Th1/Th2 Balance

The Th1/Th2 balance hypothesis, which was first described in the late 1980s,[134] has since been applied to human immunity and has become a major focus of the attempt to clarify the pathophysiology underlying the postsurgical and post-traumatic immune response.[135–137] Currently, much of the literature elevates the Th1/Th2 balance concept to the level of a paradigm.[138]

Uncommitted (naïve) CD4+ T-helper cells (Th0) can be induced to differentiate toward Th1 and Th2 phenotypes depending on the local cytokine milieu (Fig. 4). The presence of interleukin IL-12 skews toward Th1, while IL-4 tends toward Th2. The differentiation processes of Th0 to Th1 or Th2 effector cells require the action of two opposing transcription factors, T-bet and GATA-3, respectively. T-bet is essential for the development of Th1 cells, and GATA-3 performs an equivalent role in Th2 development.[139] Th1 cells drive the cellular immunity against viruses and other intracellular pathogens, eliminate cancerous cells, and stimulate delayed-type hypersensitivity skin reactions, whereas Th2 cells drive the humoral immunity and upregulate antibody production against extracellular organisms. It has been reported that after major injury, Th1 response is suppressed as illustrated by diminished IL-2, IFN-γ, and IL-12 levels, while the enhancement of the Th2 response is marked by elevated IL-10 and IL-4.[140]

Decker et al. have reported that in PBMCs derived from patients undergoing cholecystectomy, IFN-γ secretion, the index cytokine of Th1 cells, is increased, while IL-4 production, the index cytokine of Th2 cells, is decreased following surgery.[135] Heidecke et al. also reported that in patients with lethal intra-abdominal infection following surgery, T-cell proliferation and IL-2

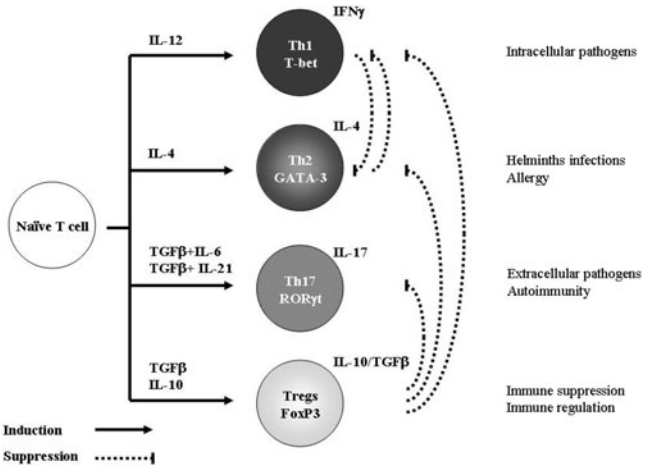

Fig. 4. Differentiation and function of T-helper cells. T-bet, GATA-3, RORγt, and FoxP3 are special transcription factors of Th1, Th2, Th17, and Tregs, respectively. Interleukin (*IL*)-12 enhances the expression of T-bet and promotes development of Th1 cells, which secrete interferon-γ (*IFN*γ) and mediate immunity to intracellular pathogens. IL-4 enhances expression of GATA-3 and promotes the development of Th2 cells, which secrete IL-4, mediate immunity to helminths, and enhance allergy. Transforming growth factor β (*TGF*β) with IL-6 or IL-21 enhances expression of RORγt and promotes development of Th17 cells, which secrete IL-17, mediate immunity to extracellular pathogens, and enhance autoimmunity. IL-10 and TGFβ promote induction of regulatory T cells (*Tregs*), which express Foxp3 and suppress immune responses. Adapted from Mills[145] and Chen and O'Shea[146]

and TNF production are severely suppressed, thus correlating with sepsis mortality, while T-cell production of IL-4 and IL-10 is not affected by postoperative intra-abdominal infections.[136] Furthermore, Zedler et al. reported that in PBMCs from patients with major burn injuries, the production of IL-4 is excessively upregulated whereas the levels of IFN-γ are only slightly increased.[137] These reports suggest that surgical or burn injury potentially induce a shift in the Th1/Th2 balance toward Th2, and that the suppression of T-cell effector functions may define a state of impaired defense against pathogens and increase susceptibility to infection and septic complications.

Interleukin-12

These alterations of T-cell response following injury have been explained at least in part by monocyte-derived cytokine IL-12.[141,142] Hensler et al. reported a prospective study of 184 patients undergoing major elective surgery of the upper and lower gastrointestinal tract, and estimated a critical role for IL-12 in human sepsis.[143] In that study, monocyte IL-12 production was severely and selectively impaired in patients developing postoperative sepsis in contrast to patients showing uneventful recovery. Moreover, the extent of monocyte IL-12 suppression correlated with the severity of postoperative sepsis. Major trauma also resulted in early and marked decrease in monocyte cytokine-producing activity.[96] Furthermore, the degree of depressed capacity of monocyte IL-12 production was statistically and significantly correlated with the development of adult respiratory distress syndrome, sepsis, or infections. These reports suggest that depression in IL-12 production by the MPS potentially promotes T-cell commitment toward a Th2 pattern resulting in postinjury septic complications, and that IL-12 is a potent immunoregulatory cytokine that is essential for the development of protective immunity.

Tregs and Th17

Tregs and Th17 cells also seem to modulate the host immune response following injury.[144–146] Th0 can differentiate not only toward Th1 and Th2, but also toward the Th17 and Treg phenotypes on the basis of the cytokine environment. The presence of IL-10 and TGF-β promotes skewing toward Treg, and TGF-β in the presence of IL-6 or IL21 promotes skewing toward Th17. Treg and Th17 are characterized by the expression of specific transcription factors: forkhead box P3 (FoxP3) for Tregs, and RORγt for Th17 cells (Fig. 4). Tregs are potent suppressors of the adaptive immune system, and Th17 cells produce a strong proinflammatory response. The skewing of murine Th0 toward Th17 and Treg is mutually antagonistic. In humans, however, there is no direct evidence for the existence of mutually exclusive development of Th17 cells and Tregs.[144–146]

Tregs have been reported to play a role in the suppression of immune reactions in patients with chronic inflammation or viral infection. In patients with Crohn's disease, FoxP3(+)CD4(+) Treg cells are expanded in mucosal lymphoid tissues and accumulate in areas of active inflammation, including granulomas and retain potent regulatory activity ex vivo.[147] Circulating and liver resident CD4+CD25+ Tregs actively influence the antiviral immune response and disease progression in patients with hepatitis B.[148] MacConmara et al. reported for the first time that in trauma patients, increased CD4+ CD25+ Tregs activity depresses protective Th1 cytokine production.[149] Furthermore, it has been reported that human CD4+CD25+FoxP3+ Tregs can induce alternative activation of monocytes/macrophages, which have strong anti-inflammatory potential involved in immune regulation, tissue remodeling, and tumor promotion.[150] Therefore, it is presumed that Tregs are potent suppressors of the innate and adaptive immune system, and play a central role in the pathogenesis of immunosuppression following surgical injury and trauma.

Many reports have provided convincing evidence that IL-17-producing T cells have been implicated in the pathogenesis of experimental and human autoimmune diseases, allograft rejection, and chronic inflammatory conditions.[144,151–154] Th17 cells function with Th1 cells to control immunity to bacteria. The major function of Th17 cells is to promote chemokine and proinflammatory cytokine production, and the subsequent recruitment and activation of neutrophils and macrophages.[145] Emerging data have suggested that in contrast to Th1 and Th2 cells, which protect against intracellular bacteria and helminths, Th17 plays an essential role in the host defense against extracellular bacteria and fungi.[146] However, the role of Th17 and IL-17 in the immune dysfunction following injury still remains poorly understood.[155]

Lymphocyte Apoptosis

In patients who died of sepsis and multiple organ dysfunction, caspase-3-mediated apoptosis has been reported to cause extensive lymphocyte apoptosis, thus contributing to an impaired immune response.[156] In addition, studies have reported that prolonged lymphopenia and apoptosis-associated depletion of lymphoid organs are involved in nosocomial sepsis-related death in critically ill children.[157] Furthermore, lymphocyte apoptosis is increased in CD4 and CD8 T cells, B cells (CD20), and NK cells (CD56) in septic patients compared to nonseptic patients.[158] The authors also demonstrated that apoptotic lymphocytes are positive for activated caspases 8 and 9, consistent with cell death occurring by both mitochondrial-mediated and receptor-mediated pathways. These reports suggest that severe infection can induce apoptosis in a broad range of lymphocyte subsets, and that both of the intrinsic/mitochondrial and extrinsic/death receptor-mediated pathways may contribute to the immune hyporesponsiveness that is seen in septic patients.[159,160]

Conclusions

A review of the literature indicates that surgical and trauma injury profoundly affects the innate and adaptive immune responses, and that marked suppression in cell-mediated immunity following an excessive inflammatory response appears to be responsible for the increased susceptibility to subsequent sepsis. The innate and adaptive immune responses are initiated and modulated not only by PAMPs, but also by DAMPs through PRRs. The suppression of cell-mediated immunity may be caused by multifaceted cytokine/inhibitor profiles in the circulation and other compartments of the host, excessive activation and dysregulated recruitment of PMNs, induction of alternatively activated or regulatory macrophages that have anti-inflammatory properties, a shift in the Th1/Th2 balance toward Th2, appearance of Tregs which are potent suppressors of the innate and adaptive immune system, and lymphocyte apoptosis in patients with sepsis. Recent basic and clinical studies have explored the functional effects of surgical and traumatic injury on the immune system. Future studies will likely contribute further valuable information that will make it possible to better select the most appropriate therapeutic protocols.

References

1. Dixon E, Vollmer CM Jr, Sahajpal A, Cattral M, Grant D, Doig C, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. Ann Surg 2005;241:385–94.
2. Shigeta H, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, et al. Bacteremia after hepatectomy: an analysis of a single-center, 10-year experience with 407 patients. Langenbecks Arch Surg 2002;387:117–24.
3. Schmidt CM, Powell ES, Yiannoutsos CT, Howard TJ, Wiebke EA, Wiesenauer CA, et al. Pancreaticoduodenectomy: a 20-year experience in 516 patients. Arch Surg 2004;139:718–25.
4. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002;236:355–66.
5. Busquets J, Fabregat J, Borobia FG, Jorba R, Valls C, Serrano T, et al. Organ-preserving surgery for benign lesions and low-grade malignancies of the pancreatic head: a matched case-control study. Surg Today 2010;40:125–31.
6. Angele MK, Chaudry IH. Surgical trauma and immunosuppression: pathophysiology and potential immunomodulatory approaches. Langenbecks Arch Surg 2005;390:333–41.
7. Ni Choileain N, Redmond HP. Cell response to surgery. Arch Surg 2006;141:1132–40.
8. Ni Choileain N, Redmond HP. The immunological consequences of injury. Surgeon 2006;4:23–31.
9. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. Injury 2007;38:1336–45.
10. Bone RC. 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 1996;125: 680–7.
11. Moore FA, Moore EE. Evolving concepts in the pathogenesis of postinjury multiple organ failure. Surg Clin North Am 1995;75: 257–77.
12. Tschoeke SK, Hellmuth M, Hostmann A, Ertel W, Oberholzer A. The early second hit in trauma management augments the proinflammatory immune response to multiple injuries. J Trauma 2007;62:1396–403.
13. Biffl WL, Moore EE, Moore FA, Peterson VM. Interleukin-6 in the injured patient. Marker of injury or mediator of inflammation? Ann Surg 1996;224:647–64.
14. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. Br J Surg 1992; 79: 757–60.
15. Gale LM, McColl SR. Chemokines: extracellular messengers for all occasions? Bioessays 1999;21:17–28.

16. Strüber M, Cremer JT, Gohrbandt B, Hagl C, Jankowski M, Völker B, et al. Human cytokine responses to coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg 1999;68:1330–5.
17. Lehmann AK, Halstensen A, Sørnes S, Røkke O, Waage A. High levels of interleukin 10 in serum are associated with fatality in meningococcal disease. Infect Immun 1995;63:2109–12.
18. Marchant A, Alegre ML, Hakim A, Piérard G, Marécaux G, Friedman G, et al. Clinical and biological significance of interleukin-10 plasma levels in patients with septic shock. J Clin Immunol 1995;15:266–73.
19. Howard M, Muchamuel T, Andrade S, Menon S. Interleukin 10 protects mice from lethal endotoxemia. J Exp Med 1993;177: 1205–8.
20. Florquin S, Amraoui Z, Abramowicz D, Goldman M. Systemic release and protective role of IL-10 in staphylococcal enterotoxin B-induced shock in mice. J Immunol 1994;153:2618–23.
21. DiPiro JT, Howdieshell TR, Goddard JK, Callaway DB, Hamilton RG, Mansberger AR Jr. Association of interleukin-4 plasma levels with traumatic injury and clinical course. Arch Surg 1995;130:1159–62.
22. Wanidworanun C, Strober W. Predominant role of tumor necrosis factor-alpha in human monocyte IL-10 synthesis. J Immunol 1993;151:6853–61.
23. Riedemann NC, Guo RF, Ward PA. Novel strategies for the treatment of sepsis. Nat Med 2003;9:517–24.
24. Offner PJ, Moore EE, Ciesla D. The adrenal response after severe trauma. Am J Surg 2002;184:649–53.
25. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 2003;167:512–20.
26. Roger T, Glauser MP, Calandra T. Macrophage migration inhibitory factor (MIF) modulates innate immune responses induced by endotoxin and Gram-negative bacteria. J Endotoxin Res 2001;7:456–60.
27. Kain ZN, Zimolo Z, Heninger G. Leptin and the perioperative neuroendocrinological stress response. J Clin Endocrinol Metab 1999;84: 2438–42.
28. Sánchez-Margalet V, Martín-Romero C, Santos-Alvarez J, Goberna R, Najib S, Gonzalez-Yanes C. Role of leptin as an immunomodulator of blood mononuclear cells: mechanisms of action. Clin Exp Immunol 2003;133:11–9.
29. Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, et al. Circulating cytokines, chemokines, and stress hormones are increased in patients with organ dysfunction following liver resection. J Surg Res 2006;133:102–12.
30. Kimura F, Miyazaki M, Suwa T, Sugiura T, Shinoda T, Itoh H, et al. Plasma concentration of cytokine antagonists in patients with infection following liver resection. Br J Surg 1998;85:1631–5.
31. Osuchowski MF, Welch K, Siddiqui J, Remick DG. Circulating cytokine/inhibitor profiles reshape the understanding of the SIRS/CARS continuum in sepsis and predict mortality. J Immunol 2006;177:1967–74.
32. Martinon F, Tschopp J. NLRs join TLRs as innate sensors of pathogens. Trends Immunol 2005;26:447–54.
33. Liew FY, Xu D, Brint EK, O'Neill LA. Negative regulation of toll-like receptor-mediated immune responses. Nat Rev Immunol 2005;5:446–58.
34. Lamkanfi M, Kanneganti TD, Franchi L, Nunez G. Caspase-1 inflammasomes in infection and inflammation. J Leukoc Biol 2007;82:220–5.
35. Kawai T, Akira S. Innate immune recognition of viral infection. Nat Immunol 2006;7:131–7.
36. Härter L, Mica L, Stocker R, Trentz O, Keel M. Increased expression of toll-like receptor-2 and -4 on leukocytes from patients with sepsis. Shock 2004;22:403–9.
37. Shalhub S, Junker CE, Imahara SD, Mindrinos MN, Dissanaike S, O'Keefe GE. Variation in the TLR4 gene influences the risk of organ failure and shock posttrauma: a cohort study. J Trauma 2009;66:115–22.
38. Carneiro LA, Magalhaes JG, Tattoli I, Philpott DJ, Travassos LH. Nod-like proteins in inflammation and disease. J Pathol 2008;214: 136–48.
39. Martinon F. Orchestration of pathogen recognition by inflammasome diversity: Variations on a common theme. Eur J Immunol 2007;37:3003–6.
40. Sutterwala FS, Ogura Y, Flavell RA. The inflammasome in pathogen recognition and inflammation. J Leukoc Biol 2007;82: 259–64.
41. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347:417–29.
42. Fahy RJ, Exline MC, Gavrilin MA, Bhatt NY, Besecker BY, Sarkar A, et al. Inflammasome mRNA expression in human monocytes during early septic shock. Am J Respir Crit Care Med 2008;177:983–8.
43. Rubartelli A, Lotze MT. Inside, outside, upside down: damage-associated molecular-pattern molecules (DAMPs) and redox. Trends Immunol 2007;28:429–36.
44. Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. J. Leukoc. Biol 2007;81:1–5.
45. Bonaldi T, Talamo F, Scaffidi P, Ferrera D, Porto A, Bachi A, et al. Monocytic cells hyperacetylate chromatin protein HMGB1 to redirect it towards secretion. EMBO J 2003;22:5551–60.
46. Wang H, Yang H, Tracey KJ. Extracellular role of HMGB1 in inflammation and sepsis. J Intern Med 2004;255:320–31.
47. Abraham E, Arcaroli J, Carmody A, Wang H, Tracey KJ. HMG-1 as a mediator of acute lung inflammation. J Immunol 2000;165: 2950–4.
48. Kim JY, Park JS, Strassheim D, Douglas I, Diaz del Valle F, Asehnoune K, et al. HMGB1 contributes to the development of acute lung injury after hemorrhage. Am J Physiol Lung Cell Mol Physiol 2005;288:L958–65.
49. Tsung A, Sahai R, Tanaka H, Nakao A, Fink MP, Lotze MT, et al. The nuclear factor HMGB1 mediates hepatic injury after murine liver ischemia-reperfusion. J Exp Med 2005;201: 1135–43.
50. Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, et al. HMG-1 as a late mediator of endotoxin lethality in mice. Science 1999;285(5425):248–51.
51. Ombrellino M, Wang H, Ajemian MS, Talhouk A, Scher LA, Friedman SG, et al. Increased serum concentrations of high-mobility-group protein 1 in haemorrhagic shock. Lancet 1999; 354(9188):1446–7.
52. Ueno H, Matsuda T, Hashimoto S, Amaya F, Kitamura Y, Tanaka M, et al. Contributions of high mobility group box protein in experimental and clinical acute lung injury. Am J Respir Crit Care Med 2004;170:1310–6.
53. Sundén-Cullberg J, Norrby-Teglund A, Rouhiainen A, Rauvala H, Herman G, Tracey KJ, et al. Persistent elevation of high mobility group box-1 protein (HMGB1) in patients with severe sepsis and septic shock. Crit Care Med 2005;33:564–73.
54. Chen W, Syldath U, Bellmann K, Burkart V, Kolb H. Human 60-kDa heat-shock protein: a danger signal to the innate immune system. J Immunol 1999;162:3212–9.
55. Ohashi K, Burkart V, Flohe S, Kolb H. Cutting edge: heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex. J Immunol 2000;164:558–61.
56. Dybdahl B, Wahba A, Lien E, Flo TH, Waage A, Qureshi N, et al. Inflammatory response after open heart surgery: release of heat-shock protein 70 and signaling through toll-like receptor-4. Circulation 2002;105:685–90.
57. Kimura F, Itoh H, Ambiru S, Shimizu H, Togawa A, Yoshidome H, et al. Circulating heat-shock protein 70 is associated with postoperative infection and organ dysfunction after liver resection. Am J Surg 2004;187:777–84.

58. Bours MJ, Swennen EL, Di Virgilio F, Cronstein BN, Dagnelie PC. Adenosine 5′-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. Pharmacol Ther 2006;112:358–404.
59. Sitkovsky MV, Ohta A. The "danger" sensors that STOP the immune response: the A2 adenosine receptors? Trends Immunol 2005;26:299–304.
60. Deaglio S, Dwyer KM, Gao W, Friedman D, Usheva A, Erat A, et al. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. J Exp Med 2007;204:1257–65.
61. van Maren WW, Jacobs JF, de Vries IJ, Nierkens S, Adema GJ. Toll-like receptor signalling on Tregs: to suppress or not to suppress? Immunology 2008;124:445–52.
62. Seely AJ, Pascual JL, Christou NV. Science review: Cell membrane expression (connectivity) regulates neutrophil delivery, function and clearance. Crit Care 2003;7:291–307.
63. Fialkow L, Wang Y, Downey GP. Reactive oxygen and nitrogen species as signaling molecules regulating neutrophil function. Free Radic Biol Med 2007;42:153–64.
64. Wakefield CH, Carey PD, Foulds S, Monson JR, Guillou PJ. Polymorphonuclear leukocyte activation. An early marker of the postsurgical sepsis response. Arch Surg 1993;128:390–5.
65. Jimenez MF, Watson RW, Parodo J, Evans D, Foster D, Steinberg M, et al. Dysregulated expression of neutrophil apoptosis in the systemic inflammatory response syndrome. Arch Surg 1997;132:1263–9.
66. Maekawa K, Futami S, Nishida M, Terada T, Inagawa H, Suzuki S, et al. Effects of trauma and sepsis on soluble L-selectin and cell surface expression of L-selectin and CD11b. J Trauma 1998;44:460–8.
67. Quaid G, Cave C, Williams MA, Hennigan RF, Bokoch G, Solomkin JS. Mechanisms of human neutrophil oxidant production after severe injury. Surgery 2001;130:669–75.
68. Foulds S, Mireskandari M, Kalu P, Jackson W, Cheshire NJ, Mansfield AO, et al. Visceral ischemia and neutrophil activation in sepsis and organ dysfunction. J Surg Res 1998;75:170–6.
69. Foulds S, Cheshire NJ, Schachter M, Wolfe JH, Mansfield AO. Endotoxin related early neutrophil activation is associated with outcome after thoracoabdominal aortic aneurysm repair. Br J Surg 1997;84:172–7.
70. Partrick DA, Moore EE, Fullerton DA, Barnett CC Jr, Meldrum DR, Silliman CC. Cardiopulmonary bypass renders patients at risk for multiple organ failure via early neutrophil priming and late neutrophil disability. J Surg Res 1999;86:42–9.
71. Bhatia R, Dent C, Topley N, Pallister I. Neutrophil priming for elastase release in adult blunt trauma patients. J Trauma 2006;60:590–6.
72. Gando S, Kameue T, Matsuda N, Sawamura A, Hayakawa M, Kato H. Systemic inflammation and disseminated intravascular coagulation in early stage of ALI and ARDS: role of neutrophil and endothelial activation. Inflammation 2004;28:237–44.
73. Inoue Y, Tanaka H, Ogura H, Ukai I, Fujita K, Hosotsubo H, et al. A neutrophil elastase inhibitor, sivelestat, improves leukocyte deformability in patients with acute lung injury. J Trauma 2006;60:936–43.
74. Gando S, Kameue T, Matsuda N, Hayakawa M, Ishitani T, Morimoto Y, et al. Combined activation of coagulation and inflammation has an important role in multiple organ dysfunction and poor outcome after severe trauma. Thromb Haemost 2002;88:943–9.
75. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nat Rev Immunol 2008;8:776–87.
76. Olson TS, Ley K. Chemokines and chemokine receptors in leukocyte trafficking. Am J Physiol Regul Integr Comp Physiol 2002;283:R7–28.
77. Reutershan J, Ley K. Bench-to-bedside review: acute respiratory distress syndrome—how neutrophils migrate into the lung. Crit Care 2004;8:453–61.
78. Villard J, Dayer-Pastore F, Hamacher J, Aubert JD, Schlegel-Haueter S, Nicod LP. GRO alpha and interleukin-8 in *Pneumocystis carinii* or bacterial pneumonia and adult respiratory distress syndrome. Am J Respir Crit Care Med 1995;152:1549–54.
79. Tsai WC, Strieter RM, Mehrad B, Newstead MW, Zeng X, Standiford TJ. CXC chemokine receptor CXCR2 is essential for protective innate host response in murine Pseudomonas aeruginosa pneumonia. Infect Immun 2000;68:4289–96.
80. Adams JM, Hauser CJ, Livingston DH, Lavery RF, Fekete Z, Deitch EA. Early trauma polymorphonuclear neutrophil responses to chemokines are associated with development of sepsis, pneumonia, and organ failure. J Trauma 2001;51:452–6.
81. Tarlowe MH, Duffy A, Kannan KB, Itagaki K, Lavery RF, Livingston DH, et al. Prospective study of neutrophil chemokine responses in trauma patients at risk for pneumonia. Am J Respir Crit Care Med 2005;171:753–9.
82. Brown KA, Brain SD, Pearson JD, Edgeworth JD, Lewis SM, Treacher DF. Neutrophils in development of multiple organ failure in sepsis. Lancet 2006;368(9530):157–69.
83. Terregino CA, Lubkin CL, Thom SR. Impaired neutrophil adherence as an early marker of systemic inflammatory response syndrome and severe sepsis. Ann Emerg Med 1997;29:400–3.
84. Arraes SM, Freitas MS, da Silva SV, de Paula Neto HA, Alves-Filho JC, Auxiliadora Martins M, et al. Impaired neutrophil chemotaxis in sepsis associates with GRK expression and inhibition of actin assembly and tyrosine phosphorylation. Blood 2006;108:2906–13.
85. Rot A, von Andrian UH. Chemokines in innate and adaptive host defense: basic chemokinese grammar for immune cells. Annu Rev Immunol 2004;22:891–928.
86. Martins PS, Kallas EG, Neto MC, Dalboni MA, Blecher S, Salomão R. Upregulation of reactive oxygen species generation and phagocytosis, and increased apoptosis in human neutrophils during severe sepsis and septic shock. Shock 2003;20:208–12.
87. Kaufmann I, Hoelzl A, Schliephake F, Hummel T, Chouker A, Peter K, et al. Polymorphonuclear leukocyte dysfunction syndrome in patients with increasing sepsis severity. Shock 2006;26:254–61.
88. Danikas DD, Karakantza M, Theodorou GL, Sakellaropoulos GC, Gogos CA. Prognostic value of phagocytic activity of neutrophils and monocytes in sepsis. Correlation to CD64 and CD14 antigen expression. Clin Exp Immunol 2008;154:87–97.
89. van der Meer W, Pickkers P, Scott CS, van der Hoeven JG, Gunnewiek JK. Hematological indices, inflammatory markers and neutrophil CD64 expression: comparative trends during experimental human endotoxemia. J Endotoxin Res 2007;13:94–100.
90. Taneja R, Sharma AP, Hallett MB, Findlay GP, Morris MR. Immature circulating neutrophils in sepsis have impaired phagocytosis and calcium signaling. Shock 2008;30:618–22.
91. Serbina NV, Jia T, Hohl TM, Pamer EG. Monocyte-mediated defense against microbial pathogens. Annu Rev Immunol 2008;26:421–52.
92. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nat Rev Immunol 2005;5:953–64.
93. Benoit M, Desnues B, Mege JL. Macrophage polarization in bacterial infections. J Immunol 2008;181:3733–9.
94. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008;8:958–69.
95. Gerber JS, Mosser DM. Reversing lipopolysaccharide toxicity by ligating the macrophage Fcγ receptors. J Immunol 2001;166:6861–8.
96. Spolarics Z, Siddiqi M, Siegel JH, Garcia ZC, Stein DS, Denny T, et al. Depressed interleukin-12-producing activity by monocytes correlates with adverse clinical course and a shift toward

Th2-type lymphocyte pattern in severely injured male trauma patients. Crit Care Med 2003;31:1722–9.
97. Weighardt H, Heidecke CD, Westerholt A, Emmanuilidis K, Maier S, Veit M, et al. Impaired monocyte IL-12 production before surgery as a predictive factor for the lethal outcome of postoperative sepsis. Ann Surg 2002;235:560–7.
98. Ditschkowski M, Kreuzfelder E, Rebmann V, Ferencik S, Majetschak M, Schmid EN, et al. HLA-DR expression and soluble HLA-DR levels in septic patients after trauma. Ann Surg 1999;229:246–54.
99. Wakefield CH, Carey PD, Foulds S, Monson JR, Guillou PJ. Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. Br J Surg 1993;80:205–9.
100. Schinkel C, Sendtner R, Zimmer S, Faist E. Functional analysis of monocyte subsets in surgical sepsis. J Trauma 1998;44:743–8.
101. Venet F, Tissot S, Debard AL, Faudot C, Crampé C, Pachot A, et al. Decreased monocyte human leukocyte antigen-DR expression after severe burn injury: Correlation with severity and secondary septic shock. Crit Care Med 2007;35:1910–7.
102. Tschaikowsky K, Hedwig-Geissing M, Schiele A, Bremer F, Schywalsky M, Schüttler J. Coincidence of pro- and anti-inflammatory responses in the early phase of severe sepsis: Longitudinal study of mononuclear histocompatibility leukocyte antigen-DR expression, procalcitonin, C-reactive protein, and changes in T-cell subsets in septic and postoperative patients. Crit Care Med 2002;30:1015.
103. Monneret G, Finck ME, Venet F, Debard AL, Bohé J, Bienvenu J, et al. The anti-inflammatory response dominates after septic shock: Association of low monocyte HLA-DR expression and high interleukin-10 concentration. Immunol Lett 2004;95:193–8.
104. Fumeaux T, Pugin J. Role of interleukin-10 in the intracellular sequestration of human leukocyte antigen-DR in monocytes during septic shock. Am J Respir Crit Care Med 2002;166:1475–82.
105. Lekkou A, Karakantza M, Mouzaki A, Kalfarentzos F, Gogos CA. Cytokine production and monocyte HLA-DR expression as predictors of outcome for patients with community-acquired severe infections. Clin Diagn Lab Immunol 2004;11:161–7.
106. Abe R, Hirasawa H, Oda S, Sadahiro T, Nakamura M, Watanabe E, et al. Up-regulation of interleukin-10 mRNA expression in peripheral leukocytes predicts poor outcome and diminished human leukocyte antigen-DR expression on monocytes in septic patients. J Surg Res 2008;147:1–8.
107. de Waal Malefyt R, Haanen J, Spits H, Roncarolo MG, te Velde A, Figdor C, et al. Interleukin 10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via down-regulation of class II major histocompatibility complex expression. J Exp Med 1991;174:915.
108. Morel AS, Coulton G, Londei M. Regulation of major histocompatibility complex class II synthesis by interleukin-10. Immunology 2002;106:229–36.
109. Aste-Amezaga M, Ma X, Sartori A, Trinchieri G. Molecular mechanisms of the induction of IL-12 and its inhibition by IL-10. J Immunol 1998;160:5936–44.
110. Randow F, Syrbe U, Meisel C, Krausch D, Zuckermann H, Platzer C, et al. Mechanism of endotoxin desensitization: involvement of interleukin 10 and transforming growth factor beta. J Exp Med 1995;181:1887–92.
111. Döcke WD, Randow F, Syrbe U, Krausch D, Asadullah K, Reinke P, et al. Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. Nat Med 1997;3:678–81.
112. Astiz M, Saha D, Lustbader D, Lin R, Rackow E. Monocyte response to bacterial toxins, expression of cell surface receptors, and release of anti-inflammatory cytokines during sepsis. J Lab Clin Med 1996;128:594–600.
113. Sfeir T, Saha DC, Astiz M, Rackow EC. Role of interleukin-10 in monocyte hyporesponsiveness associated with septic shock. Crit Care Med 2001;29:129–33.
114. Tsujimoto H, Ono S, Majima T, Efron PA, Kinoshita M, Hiraide H, et al. Differential toll-like receptor expression after ex vivo lipopolysaccharide exposure in patients with sepsis and following surgical stress. Clin Immunol 2006;119:180–7.
115. Schaaf B, Luitjens K, Goldmann T, van Bremen T, Sayk F, Dodt C, et al. Mortality in human sepsis is associated with downregulation of Toll-like receptor 2 and CD14 expression on blood monocytes. Diagn Pathol 2009;4:12.
116. Re F, Strominger JL. IL-10 Released by concomitant TLR2 stimulation blocks the induction of a subset of Th1 cytokines that are specifically induced by TLR4 or TLR3 in human dendritic cells. J Immunol 2004;173:7548–55.
117. Tamandl D, Bahrami M, Wessner B, Weigel G, Ploder M, Furst W, et al. Modulation of toll-like receptor 4 expression on human monocytes by tumor necrosis factor and interleukin-6: tumor necrosis factor evokes lipopolysaccharide hyporesponsiveness, whereas interleukin-6 enhances lipopolysaccharide activity. Shock 2003;20:224–9.
118. Salomao R, Brunialti MK, Gomes NE, Mendes ME, Diaz RS, Komninakis S, et al. Toll-like receptor pathway signaling is differently regulated in neutrophils and peripheral mononuclear cells of patients with sepsis, severe sepsis, and septic shock. Crit Care Med 2009;37:132–9.
119. Martins PS, Brunialti MK, Martos LS, Machado FR, Assunçao MS, Blecher S, et al. Expression of cell surface receptors and oxidative metabolism modulation in the clinical continuum of sepsis. Crit Care 2008;12:R25.
120. Zughaier SM, Shafer WM, Stephens DS. Antimicrobial peptides and endotoxin inhibit cytokine and nitric oxide release but amplify respiratory burst response in human and murine macrophages. Cell Microbiol 2005;7:1251–62.
121. Wolkow PP. Involvement and dual effects of nitric oxide in septic shock. Inflamm Res 1998;47(4):152–66.
122. Cauwels A, Brouckaert P. Survival of TNF toxicity: dependence on caspases and NO. Arch Biochem Biophys 2007;462:132–9.
123. Bultinck J, Sips P, Vakaet L, Brouckaert P, Cauwels A. Systemic NO production during (septic) shock depends on parenchymal and not on hematopoietic cells: in vivo iNOS expression pattern in (septic) shock. FASEB J 2006;20:2363–5.
124. Annane D, Sanquer S, Sébille V, Faye A, Djuranovic D, Raphaël JC, et al. Compartmentalised inducible nitric-oxide synthase activity in septic shock. Lancet 2000;355(9210):1143–8.
125. Hirabayashi N, Tanimura H, Yamaue H. Nitrite/nitrate oxide and cytokines changes in patients with surgical stress. Dig Dis Sci 2005;50:893–7.
126. Novotny AR, Emmanuel K, Maier S, Westerholt A, Weighardt H, Stadler J, et al. Cytochrome P450 activity mirrors nitric oxide levels in postoperative sepsis: predictive indicators of lethal outcome. Surgery 2007;141:376–84.
127. Kobayashi A, Hashimoto S, Kooguchi K, Kitamura Y, Onodera H, Urata Y, et al. Expression of inducible nitric oxide synthase and inflammatory cytokines in alveolar macrophages of ARDS following sepsis. Chest 1998;113:1632–9.
128. Tsukahara Y, Morisaki T, Horita Y, Torisu M, Tanaka M. Expression of inducible nitric oxide synthase in circulating neutrophils of the systemic inflammatory response syndrome and septic patients. World J Surg 1998;22:771–7.
129. Weinberg JB, Misukonis MA, Shami PJ, Mason SN, Sauls DL, Dittman WA, et al. Human mononuclear phagocyte inducible nitric oxide synthase (iNOS): analysis of iNOS mRNA, iNOS protein, biopterin, and nitric oxide production by blood monocytes and peritoneal macrophages. Blood 1995;86:1184–95.
130. Tashiro T, Yamamori H, Takagi K, Hayashi N, Furukawa K, Nitta H, et al. Changes in immune function following surgery for esophageal carcinoma. Nutrition 1999;15:760–6.

131. Faist E, Kupper TS, Baker CC, Chaudry IH, Dwyer J, Baue AE. Depression of cellular immunity after major injury. Its association with posttraumatic complications and its reversal with immunomodulation. Arch Surg 1986;121:1000–5.
132. O'Mahony JB, Palder SB, Wood JJ, McIrvine A, Rodrick ML, Demling RH, et al. Depression of cellular immunity after multiple trauma in the absence of sepsis. J Trauma 1984;24:869–75.
133. McIrvine AJ, O'Mahony JB, Saporoschetz I, Mannick JA. Depressed immune response in burn patients: use of monoclonal antibodies and functional assays to define the role of suppressor cells. Ann Surg 1982;196:297–304.
134. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 1986;136:2348–57.
135. Decker D, Schondorf M, Bidlingmaier F, Hirner A, von Ruecker AA. Surgical stress induces a shift in the type-1/type-2 T-helper cell balance, suggesting down-regulation of cell-mediated and up-regulation of antibody-mediated immunity commensurate to the trauma. Surgery 1996;119:316–25.
136. Heidecke CD, Hensler T, Weighardt H, Zantl N, Wagner H, Siewert JR, et al. Selective defects of T lymphocyte function in patients with lethal intra-abdominal infection. Am J Surg 1999;178:288–92.
137. Zedler S, Bone RC, Baue AE, von Donnersmarck GH, Faist E. T-cell reactivity and its predictive role in immunosuppression after burns. Crit Care Med 1999;27:66–72.
138. Kidd P. Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease. Altern Med Rev 2003;8:223–46.
139. Hwang ES, Szabo SJ, Schwartzberg PL, Glimcher LH. T helper cell fate specified by kinase-mediated interaction of T-bet with GATA-3. Science 2005;307:430–3.
140. Miller AC, Rashid RM, Elamin EM. The "T" in trauma: the helper T-cell response and the role of immunomodulation in trauma and burn patients. J Trauma 2007;63:1407–17.
141. O'Garra A, Arai N. The molecular basis of T helper 1 and T helper 2 cell differentiation. Trends Cell Biol 2000;10:542–50.
142. O'Suilleabhain C, O'Sullivan ST, Kelly JL, Lederer J, Mannick JA, Rodrick ML. Interleukin-12 treatment restores normal resistance to bacterial challenge after burn injury. Surgery 1996;120: 290–6.
143. Hensler T, Heidecke CD, Hecker H, Heeg K, Bartels H, Zantl N, et al. Increased susceptibility to postoperative sepsis in patients with impaired monocyte IL-12 production. J Immunol 1998;161:2655–9.
144. Afzali B, Lombardi G, Lechler RI, Lord GM. The role of T helper 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. Clin Exp Immunol 2007; 148:32–46.
145. Mills KH. Induction, function and regulation of IL-17-producing T cells. Eur J Immunol 2008;38:2636–49.
146. Chen Z, O'Shea JJ. Th17 cells: a new fate for differentiating helper T cells. Immunol Res 2008;41:87–102.
147. Saruta M, Yu QT, Fleshner PR, Mantel PY, Schmidt-Weber CB, Banham AH, et al. Characterization of FOXP3+CD4+ regulatory T cells in Crohn's disease. Clin Immunol 2007;125:281–90.
148. Xu D, Fu J, Jin L, Zhang H, Zhou C, Zou Z, et al. Circulating and liver resident CD4+CD25+ regulatory T cells actively influence the antiviral immune response and disease progression in patients with hepatitis B. J Immunol 2006;177:739–47.
149. MacConmara MP, Maung AA, Fujimi S, McKenna AM, Delisle A, Lapchak PH, et al. Increased CD4+ CD25+ T regulatory cell activity in trauma patients depresses protective Th1 immunity. Ann Surg 2006;244:514–23.
150. Tiemessen MM, Jagger AL, Evans HG, van Herwijnen MJ, John S, Taams LS. CD4+CD25+Foxp3+ regulatory T cells induce alternative activation of human monocytes/macrophages. Proc Natl Acad Sci USA 2007;104:19446–51.
151. Korn T, Anderson AC, Bettelli E, Oukka M. The dynamics of effector T cells and Foxp3+ regulatory T cells in the promotion and regulation of autoimmune encephalomyelitis. J Neuroimmunol 2007;191:51–60.
152. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, et al. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. Nature 2007;445(7128):648–51.
153. Loong CC, Hsieh HG, Lui WY, Chen A, Lin CY. Evidence for the early involvement of interleukin 17 in human and experimental renal allograft rejection. J Pathol 2002;197: 322–32.
154. Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 2003;52:65–70.
155. Frangen TM, Bogdanski D, Schinkel C, Roetman B, Kälicke T, Muhr G, et al. Systemic IL-17 after severe injuries. Shock 2008; 29(4):462–7.
156. Hotchkiss RS, Tinsley KW, Swanson PE, Schmieg RE Jr, Hui JJ, Chang KC, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. J Immunol 2001;166:6952–63.
157. Felmet KA, Hall MW, Clark RS, Jaffe R, Carcillo JA. Prolonged lymphopenia, lymphoid depletion, and hypoprolactinemia in children with nosocomial sepsis and multiple organ failure. J Immunol 2005;174:3765–72.
158. Hotchkiss RS, Osmon SB, Chang KC, Wagner TH, Coopersmith CM, Karl IE. Accelerated lymphocyte death in sepsis occurs by both the death receptor and mitochondrial pathways. J Immunol 2005;174:5110–8.
159. Wesche DE, Lomas-Neira JL, Perl M, Chung CS, Ayala A. Leukocyte apoptosis and its significance in sepsis and shock. J Leukoc Biol 2005;78:325–37.
160. Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. Nat Rev Immunol 2006;6: 813–22.