Bruno Riou, M.D., Ph.D., Editor

Innate Immune Dysfunction in Trauma Patients

From Pathophysiology to Treatment

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SEVERE trauma is a leading cause of death in young healthy individuals. Despite significant advances in the fields of resuscitation and modern intensive care medicine, infection remains the most frequent cause of poor outcome in severely injured patients. Osborn *et al.* have demonstrated that sepsis, and particularly ventilator-associated pneumonia, were associated with a significant increase in mortality after severe trauma.[1] In the same study, septic trauma patients also presented an increased intensive care unit length of stay as compared with patients without infection (21.8 *vs.* 4.7 days, $P < 0.001$). A marked depression of cell-mediated immune function, so-called "posttraumatic immunosupression," occurs after trauma and appears to contribute to poor clinical outcome.

Current Knowledge Regarding Innate Immune Response against Pathogens

An important function of the innate immune system is the recognition of pathogens by macrophages, neutrophils, epithelial cells, and other cell populations that directly interact with microbial antigens. These cells face a challenging situation because bacterial pathogens are heterogenous and can mutate extremely rapidly. The innate immune response has two main functions (fig. 1). The first function is to induce phagocytosis and kill off the infectious agent at the site of infection so as to avoid systemic spread of the infection. The second function is to activate the adaptive immunity to generate a long-lasting immune response against pathogens. The crucial step for initiation of an adaptive immune response lies in the activation of antigen-presenting cells (APCs) and on the capacity of APCs to present antigens to T lymphocytes.[2]

First Step: Recognition of Pathogens

The innate immune response is not dedicated to recognizing each individual structure of a pathogen (antigens), but rather to focus on specific highly conserved structures present in large groups of microorganisms that engage a limited number of receptors. These microbial structures are referred to as pathogen-associated molecular patterns (PAMP). The best-known examples of PAMPs are bacterial lipopolysaccharide, peptidoglycan, microbial lipoproteins, bacterial DNA, double-stranded RNA, and glucans. PAMPs share three common characteristics: they are exclusively produced by pathogens; they are essential for the survival and/or virulence of microorganisms and are thus highly conserved within phylogenic evolution of pathogens; and they present molecular structures shared by entire classes of pathogens.

Second Step: Activation of Adaptive Immunity

After the uptake and phagocytosis of a pathogen, proteins of the microorganisms are processed to produce antigenic peptides, which form a complex with major-histocompatibility-complex class II molecules (human leukocyte antigen [HLA]-DR molecules) on the surface of the APCs. These peptides are recognized by T-cell receptors of CD4+ lymphocytes. However, the activation of T cells requires at least two signals: the first is the complex of a peptide and a HLA-DR molecule recognized by the T-cell receptors, and the second is a costimulatory signal (CD80 and CD86 molecules) expressed on the membrane of the APCs, with this signal being recognized by the CD28 molecule on the T lymphocyte (fig. 1). Recognition of an antigen without

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Received from the Service d'Anesthésie Réanimation chirurgicale, Nantes, France. Submitted for publication September 6, 2011. Accepted for publication April 19, 2012. Support was provided solely from institutional and/or departmental sources. The figures were redrawn by Annemarie B. Johnson, C.M.I., Medical Illustrator, Wake Forest University School of Medicine Creative Communications, Wake Forest University Medical Center, Winston-Salem, North Carolina.

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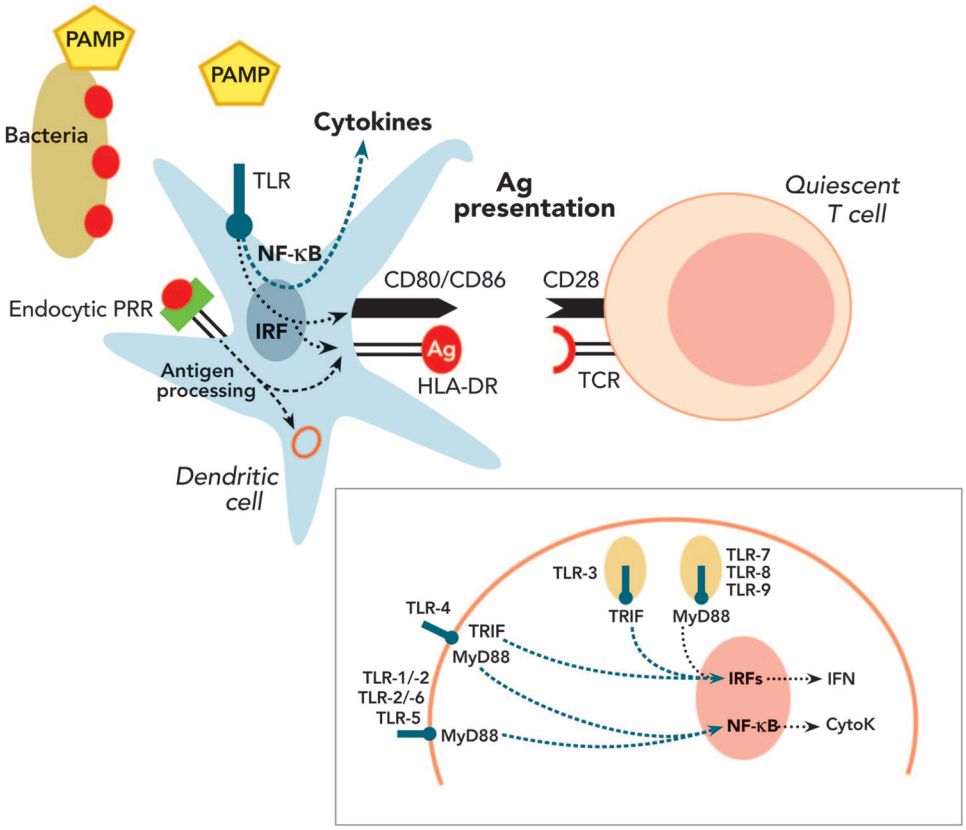

Fig. 1. Functions of dendritic cells. Pathogen-associated molecular patterns, expressed by bacteria, are recognized by toll-like receptors. Activation of the toll-like receptor signaling pathways induces expression of nuclear factor κB-dependent cytokines and interferon regulatory factor-dependent costimulatory molecules, CD80 and CD86. Pattern-recognition receptors mediate the phagocytosis of pathogens by DCs. Proteins derived from the microorganisms are processed to generate antigens. The major-histocompatibility-complex class II molecules present Ag to the T-cell receptor, activating T cells. Recognition of the co-stimulatory molecules (CD80 and CD86) by CD28 on T cell membrane is required to fully activate T cells. Ag = antigens; CD80, CD86 = costimulatory molecules; DC = dendritic cell; HLA-DR = histocompatibility-complex class II molecules; IRF = interferon regulatory factor; NF-κB = nuclear factor κB; PAMP = pathogen-associated molecular patterns; PPR = pattern-recognition receptors; TCR = T-cell receptor; TLR = toll-like receptors.

membrane expression of CD80 or CD86 molecules leads to inactivation or apoptosis of T cells. The membrane expression of CD80 and CD86 molecules depends on the activation of APCs. The recognition of PAMP by pattern recognition receptors (PRRs) induces the maturation of APCs and therefore increases the membrane expression of costimulatory molecules, including CD80 and CD86.

The production of cytokines (including interleukins, or IL-6, IL-10, IL-12, and interferon type I and II) and chemokines (such as IL-8) in response to the recognition of PAMP by PRRs also participates in the activation of both innate and adaptive immunity. These pleiotropic mediators aim to recruit immune cells into the site of infection to induce maturation and multiplication of phagocytes, APCs, and lymphocytes.

Innate Immune Receptors (PRRs)

The receptors of the innate immune system that evolved to recognize PAMPs are called PRRs.[3] The best characterized receptors are the toll-like receptors (TLRs).

TLRs, Major Players in the Battle against Pathogens. Among the PPR family, TLRs are critical in recognizing pathogens and activating the adaptive immune response. TLRs recognize conserved molecular products derived from several types of pathogens, including bacteria, DNA and RNA viruses, fungi, and protozoa. The 10 members of the TLR family are critical in sensing PAMPs. TLR2 is involved in the recognition of Gram-positive and Gram-negative bacteria. TLR4 is necessary for lipopolysaccharide signaling. TLR9 is an intracellular receptor for unmethylated bacterial DNA.

TLRs are characterized by an extracellular leucine-rich repeat domain and a cytoplasmic toll-IL-1 receptor (TIR) domain. This TIR domain shares similarities with the IL-1 receptor cytoplasmic domain. Signal transduction after interactions with PAMPs includes activation of adaptor proteins, including myeloid differentiation protein (MYD) 88. MYD88 activates kinases downstream to most TLRs and leads to the activation of nuclear factor κB (NF-κB). TIR receptor domain-containing adaptor protein inducing inter-

feron β (TRIF) is another adaptor that is critical for the production of type I interferons (interferon β or α) through activation of a family of transcription factors named interferon regulatory factors (IRFs). TRIF is engaged after TLR3 and TLR4 activation, and stimulates IRF3 and IRF7 as well as a NF-κB pathway with relatively delayed activation. Engagement of TLR7 and TLR9 induces a specific MYD88-dependent signaling pathway that activates IRF7 leading to a type I interferon production. The IRF pathway is critical for the regulation of HLA-DR and for the expression of costimulatory molecules (CD80/CD86). All TLRs except TLR3 recruit a MYD88-dependent signaling pathway leading to NF-κB expression of inflammatory mediators including inflammatory cytokines.

NF-κB regulation may be crucial in trauma, because of the presence of binding elements in the enhancer and promoter regions of proinflammatory cytokine genes, such as tumor necrosis factor-α, IL-1β, IL-6, and IL-8. NF-κB is activated by extracellular signals present in trauma patients, such as reactive oxygen species, cytokines, endotoxin, and complement fragments.[4] Cytoplasmic molecules (including IL-1 receptor-associated kinase M, and suppressor of cytokine signaling 1) negatively regulate signaling cascades leading to NF-κB activation that are induced after engagement of TLRs.

NOD-like Receptors. Nucleotide oligomerization domain (NOD) proteins are intracellular PRRs. The most studied NODs are NOD1 and NOD2. These NODs are localized in the cytoplasm and sense degradation products of bacterial cell wall components. NOD1 detects a peptidoglycan fragment present mainly on Gram-negative bacteria, whereas the NOD2 ligand is a muramyl dipeptide, a peptide shared by both Gram-positive and Gram-negative bacteria. NOD1 and NOD2 activate NF-κB as well as mitogen-activated protein kinases leading to the production of inflammatory mediators, including cytokines.

Peptidoglycan Recognition Proteins. Peptidoglycan recognition proteins (PGRPs), a third family of PRRs, has been characterized in humans and other species. Three PGRP proteins are anchored to the cytoplasmic membrane (PGRP-Ia, PGRP-Ib, and PGRP-IL), whereas the fourth PGRP is a soluble molecule (PGRP-S). The PGRP family senses peptidoglycans, which are important components of the Gram-positive bacterial cell wall. In insects, PGRPs are critical in inducing the production of antimicrobial peptides. Studies in mammals don't support a direct role for these proteins in directly sensing peptidoglycans. Their exact role in humans remains to be fully elucidated.

C-type Lectins

This family of proteins recognizes carbohydrates and is therefore critical in sensing fungal and mycobacterial infections through a carbohydrate recognition domain. Three members of this family have been described in humans: Dectin-1, Dectin-2, and Mincle. This family of proteins appears to be important in inflammatory responses associated with infections because of *Pneumocystis carinii*, *C. Albicans*, and *Aspergillus Fumigatus.* Dectin-1 and Dectin-2 also play a role in the control of respiratory infection associated with *Mycobacterium tuberculosis.*

Endogenous Mediators Activate Immune Response through PRRs

It is well known that tissue injury, including trauma, induces inflammation that clinically resembles sepsis.[5] Injured tissues, as well as necrotic cells, are responsible for such "aseptic inflammation" that may lead to multiple organ dysfunctions.

Intracellular components released after injury are called danger-associated molecular patterns (DAMPs). DAMPs have been shown to stimulate innate immunity through PRRs. These molecules activate innate immune response in the "aseptic" inflammatory response. DAMPs are most commonly nuclear, mitochondrial, or cytosolic proteins. These molecules are released in the tissues or blood after injuries and activate the immune response. Although innate response to DAMPs is critical for tissue repair, fine-tuning is mandatory to avoid DAMP-induced organ injury. Aseptic inflammation resembles inflammation associated with infections, and a study by Textoris *et al.*[6] in 165 severe trauma patients could not find any transcriptional signature to diagnose or to differentiate bacterial pneumonia from aseptic inflammation. Differentiating aseptic inflammation from infection may prove important, because giving antibiotics for aseptic inflammation could have a negative impact on bacterial ecology by increasing the rate of multiple drug-resistant bacteria.

The DAMPs with the highest cytoplasmic concentrations are heat-shock proteins.[5] Heat-shock proteins promote antigen presentation, and the maturation of dentritic cells (DC). There is increasing evidence suggesting an important role for the TLR-MYD88-NF-κB pathway (classic pathway for PAMPs) in heat-shock protein recognition. Host mitochondrial DNA shares similarities with bacterial DNA; in particular, the mitochondrial genome contains CpG DNA motifs that can activate TLR9. It has been demonstrated that the release of such mitochondrial DAMPS (MTDs) by injured cells is a major cause of systemic inflammatory response in trauma patients.[7] In this study, MTDs were involved in PMN Ca2+ flux as well as in the activation of mitogen-activated protein kinases inducing migration and activation of PMN. This activation of PMNs with MTDs may play a major role in PMN-induced organ injury. MDPs may therefore be an attractive target for reducing trauma-induced organ dysfunction

High mobility group box 1 (HMGB1) is a late mediator of the inflammatory response in sepsis. In a murine model of hemorrhage, HMGB1 was a mediator for organ dysfunction.[8] In a large cohort of trauma patients, HMGB1 expression was shown to be down-regulated at the onset of pneumonia.[6] The regulation of HMGB1 seems different in sepsis and trauma, but data are lacking to indicate if HMGB1

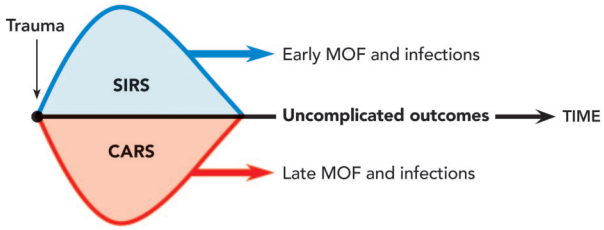

Fig. 2. Trauma-induced injury actives innate immune responses to produce pro- and antiinflammatory cytokines. Imbalance between the systemic inflammatory response syndrome and the compensatory antiinflammatory response (immunosupression) increases morbidity of trauma patients. In the first hours, the magnitude of the systemic inflammatory response syndrome is correlated with early multiple organ failure and infections. In the following days, immunosupression contributes to the increased incidence of nosocomial infections and late sepsis. CARS = compensatory anti-inflammatory response; MOF = multiple organ failure; SIRS = systemic inflammatory response syndrome.

could be a marker of prognosis or a future therapeutic target in trauma patients.

Innate Immune Dysfunction Contributes to Infection after Severe Trauma

A simultaneous imbalance of proinflammatory/antiinflammatory responses is associated with the acquisition of nosocomial infection in trauma patients. The overwhelming antiinflammatory response (compensatory antiinflammatory response) leading to immunosupression contributes to posttraumatic susceptibility to secondary infections (fig. 2). Immunosuppression following severe injury is characterized by the three following features: (1) decreased capacity of patients' leukocytes to produce proinflammatory cytokines (tumor necrosis factor-α, IL-1ß, IL-6, IL-8, and interferon) in response to endotoxin *ex vivo*[4]; (2) decreased capacity of monocytes to present antigens as assessed by the loss of HLA-DR membrane expression[9]; and (3) high blood and tissue concentrations of antiinflammatory cytokines, including IL-10.

Posttraumatic Systemic Inflammatory Response Syndrome

An intense systemic inflammatory response develops in the first hours of trauma. The inflammatory response of the host is critical for both healing from injury and for bacterial clearance during infection. However, an excessive release of proinflammatory mediators can be harmful and may promote organ dysfunction after trauma. It was demonstrated that a persistent overwhelming inflammatory response was predictive of nosocomial infections,[10] and patients that develop trauma-related corticosteroid insufficiency are particularly exposed to an excessive and prolonged systemic inflammatory response.[11] Adrenal dysfunction may be, therefore, a risk factor for nosocomial infection after trauma.

Posttraumatic Immunosuppression

The mechanisms explaining the immunosuppression after trauma or sepsis are not fully understood, and the role of the microenvironment of immune cells has received little attention. Belikova *et al.*[12] demonstrated in septic shock patients that energetic failure of peripheral blood mononuclear cells may be a factor contributing to the dysregulation of the immune response. In a recent genomic study,[13] the authors demonstrated that the early leukocyte genomic response involved genes of the innate immune response and of the compensatory antiinflammatory response; interestingly, genes involved in adaptive immunity were suppressed.[13] Finally, organ dysfunctions as well as alteration in immune and metabolic responses after trauma are generally reversible.

Decreased Capacity of Patients' Leukocytes to Produce Proinflammatory Cytokines. In trauma patients, the capacity of blood monocytes to produce proinflammatory cytokines is impaired *in vitro* after lipopolysaccharide challenge.[4] The mechanisms of this "endotoxin tolerance" remain poorly understood. The expression of TLR4, the PRR specialized in lipopolysaccharide recognition, is profoundly decreased on the surface of APCs from injured patients.[9] The expression of the lipopolysaccharide receptor CD14 on monocytes is also decreased after trauma, with this alteration accompanied by an increase of the soluble molecule CD14 (sCD14) in the serum of trauma patients.[14] Increased expression of antiinflammatory mediators like IL-10 or transforming growth factor-β following severe injury is probably involved in a decreased activity of transcription factors such as NF-κB. These long-term impaired alterations of the TLR/NF-κB signaling pathway were correlated with a poor outcome in trauma patients.[4]

Alterations of Antigen Presentation. Major surgery and severe injuries may lead to decreased expression of HLA-DR on monocytes as compared with that present in healthy volunteers. This alteration contributes to the inability of APCs to present antigen to lymphocytes following trauma. Lukaszewicz *et al.*[15] reported the HLA-DR expression patterns in a database of intensive care unit patients, including a large number of trauma patients. Other authors confirmed the relationship between secondary infection and persistent reduced HLA-DR expression in trauma patients.[16] Decreased monocyte HLA-DR expression is currently the only marker of immunosuppression that consistently correlates with secondary infections and other outcomes, such as time on ventilator and intensive care unit length of stay. The impact of monocytic HLA-DR expression on mortality remains controversial.

Patients with decreased expression of HLA-DR may benefit from specific strategies in an attempt to decrease the infectious risk: strict screening for infection, limitation of the use of invasive devices, limiting cross transmission, and possibly immunostimulating therapies. HLA-DR molecules are required but are not sufficient for antigen presentation to T cells. Indeed, the recognition of the antigen-HLA-DR com-

plex by T-cell receptors without costimulation (CD80/86 expression) leads to anergy or apoptosis of T cells. A decrease in CD80 and/or CD86 membrane expression on APCs could therefore participate in posttraumatic immunosuppression. This issue is poorly studied, and to date, no data are available concerning trauma patients.

Brain Injury Plays a Major Role in Posttraumatic Immunosuppression

In the setting of severe trauma, patients with brain injuries display an increased rate of secondary infections that appear to be correlated with severe impairment of immune function, perhaps secondary to alterations in autonomic nervous system function. Woiciechowsky *et al.* in neurosurgical patients demonstrated that a "catecholinergic storm" was responsible for monocytic deactivation through IL-10 release.[17] Interestingly, in a study by Lukaszewicz *et al.*, monocytic deactivation (decreased HLA-DR expression) was not correlated with any modification of IL-10 but rather with altered release of neuromediators.[18] These data are in line with recent data confirming the critical importance of central sympathetic activation in immunosuppession after brain injury.[19] Finally, it should be mentioned that patients are heavily sedated after traumatic brain injury, and many drugs, such as barbiturates and midazolam, alter immune function.[20]

Implications for Immunointervention in Trauma Patients[21]

Data obtained in animal models and in the clinical setting suggest it may be beneficial to treat the severe immunosuppression encountered after sepsis or trauma in an attempt to decrease septic complications or mortality.[21,22]

DCs, Key Cells of Innate Immunity for Immune Intervention[23]. DCs are the most potent APCs of the immune system, and are the only APC capable of activating naive T cells. DCs are therefore critical in linking innate and adaptive immunity and are likely to be an important cell population for immunointervention against infections after trauma. Indeed, there is a growing body of evidence showing that DCs play a major role in inducing resistance to infection. For example, in a murine model of hemorrhage, preventive treatment with CpG-ODN (a TLR-9 agonist) or monophosphoryl Lipid A (a TLR-4 agonist) increased the transcriptional activity of tumor necrosis factor-α, interferon-β, and IL-12p40 in DCs and was associated with decreased mortality from posthemorrhage methicillin-sensitive *Staphylococcus aureus* pneumonia.[22] DCs are important cells for resistance to viruses, such as cytomegalovirus or dengue virus, as well as for resistance to bacterial sepsis.[23] In septic patients, alterations in the microenvironment enhance the differentiation of blood monocytes into DCs *in vitro*, without accelerating their ability to activate T cells.[24] Targeting the microenvironment might therefore be an approach to treat posttraumatic immunosuppression.

Clinical Trials

A systematic review recently explored randomized controlled trials using immune interventions.[21] Interferon-γ, intravenous immunoglobulins, and glucans were considered to be the most promising drugs for improving mortality as well as organ failure. However, the studies analyzed were generally performed more than 10 yr ago and are from a single center, and the results were not confirmed in more recent clinical trials.[21] It has been suggested that hydrocortisone may attenuate the overwhelming inflammatory response without inducing immunosuppression.[24] These beneficial effects on the innate immune response of the host could restore an adequate response to infection. In septic shock patients, low doses of hydrocortisone increased the phagocytic capacities of monocytes and the production of the monocyte-activating cytokine IL-12 when decreasing the IL-10 production.[25] We recently demonstrated that low doses of hydrocortisone decreased the risk of hospital-acquired pneumonia as well as the duration of mechanical ventilation[26] in severely ill patients, probably by restoring adequate immune function.

Conclusion

Innate immunity is the first step of host defense against infection. The PPRs, which are sensors of innate immune cells for microorganisms, are essential for activation of adaptive immunity (antigen presentation) and for control of the inflammatory/antiinflammatory balance (cytokine production). Recent insights into posttraumatic immune dysfunction have defined new targets for immunointervention and prevention of nosocomial infection after trauma. However, there are no convincing data to support any immune intervention at the present time. The lack of evidence for efficacy of immunotherapies in trauma may reflect the heterogeneity of immune and cellular activation responses in injured patients and our inability to appropriately discriminate patients that would benefit from these interventions from those patients who would not. There is an urgent need to develop assays and to identify biomarkers that will allow physicians to accurately treat immunosuppression, based on specific immunologic profiles.

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