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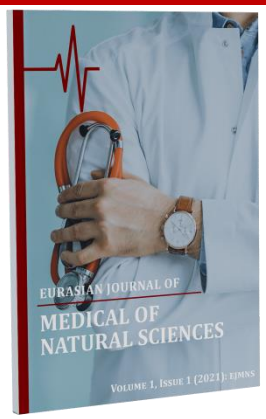

IMMUNE RESPONSE TO TRAUMATIC INJURY: BALANCE AND DISRUPTION OF IMMUNE SYSTEM HOMEOSTASIS

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ABSTRACT

Trauma is a leading cause of death globally, disrupting immune system balance and potentially causing infections and inflammatory issues. A major challenge is preventing multiple organ dysfunction syndrome (MODS) due to septic complications following severe trauma. Typically, after a severe injury, the immune system shifts from a pro-inflammatory to a counter-inflammatory state, which is seen as a protective response to balance the innate and adaptive immune systems. Our research shows that injury activates inflammasomes and primes Toll-like receptors, enhancing the innate immune system's antimicrobial defense. However, trauma can also cause a "two-hit" response. Additionally, we found that injury increases regulatory T cell activity, which can influence this "two-hit" response. This paper explores how traumatic injury triggers a unique immune response, possibly initiated by damage-associated molecular pattern molecules (DAMPs), a mix of endogenous danger signals, including alarmins and pathogen-associated molecular pattern molecules (PAMPs).

Introduction

Trauma is a major cause of death worldwide, with the timing of fatalities following a trimodal distribution. The first phase includes immediate deaths at the scene or within the first hour, often due to heart rupture, cervical spine disruption, or massive exencephaly. The second phase involves deaths within 24 hours, mainly from hemorrhagic shock. The third, late phase occurs typically a week or more after the injury, primarily due to infectious complications such as sepsis, septic shock, and multiple organ dysfunction syndrome (MODS). Around 10% of trauma patients develop sepsis, which is linked to the severity of injury and greatly increases mortality compared to non-septic patients.

Why do patients succumb to sepsis more than a week after injury? This question is tied to how injury impacts the immune system, making individuals more susceptible to opportunistic infections and complications. The immune system is crucial in defending against infections and managing tissue injury and cell death in burns and trauma. Injury

activates the immune system, enhancing innate immune reactivity, controlling excessive pro-inflammatory responses, and reducing ongoing tissue damage. Thus, trauma causes dynamic changes in immune system behavior, marked by pro-inflammatory and counter-inflammatory responses. The pro-inflammatory response is mainly driven by the innate immune system, while the counter-inflammatory response is managed by the adaptive immune system. Clinically, these responses are known as systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS), and mixed anti-inflammatory response syndrome (MARS).

Initiation of the Immune Response by Injury

Trauma causes significant tissue damage, resulting in the release of various antigens and mediators. These endogenous factors, known as alarmins, act as danger signals that alert the immune system to the trauma. Alarmins interact with immune cells, triggering inflammatory responses. A comprehensive overview of trauma-associated alarmins has been documented previously. Figure 1 illustrates the initiation of the innate immune system following trauma. Pattern recognition receptors, such as Toll-like receptors (TLRs), detect alarmins and exogenous antigens known as pathogen-associated molecular pattern molecules (PAMPs). This combination of endogenous (alarmins) and exogenous (PAMPs) danger signals forms what is called damage-associated molecular pattern molecules. After trauma, patients are exposed to alarmins that activate the immune system to protect against tissue injury and microbial invasion. However, a primed immune system may result in excessive inflammation, known as a "two-hit" response phenotype, as further discussed in Figure 2.

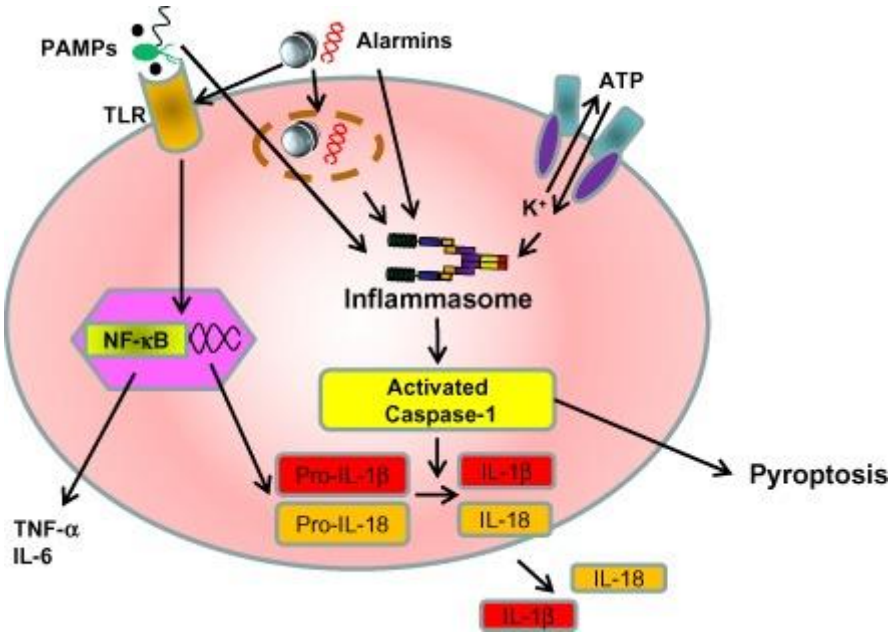

Figure 1

The immune system activation pathway following injury involves the inflammasome, a large multiprotein complex that plays a critical role in innate immunity by aiding in the production of pro-inflammatory cytokines such as interleukin (IL)-1β and IL-18. These cytokines are initially produced as inactive precursors, pro-IL-1β and pro-IL-18, and require activated caspase-1 for maturation. Inflammasomes detect damage-associated molecular

patterns, including pathogen-associated molecular patterns (PAMPs) and host-derived signals known as alarmins. The cell death induced by inflammasome activation is called pyroptosis. Alarmins also activate Toll-like receptors (TLRs), which produce IL-6 and tumor necrosis factor (TNF)-α in response to injury, involving the nuclear factor-κB (NF-κB) pathway.

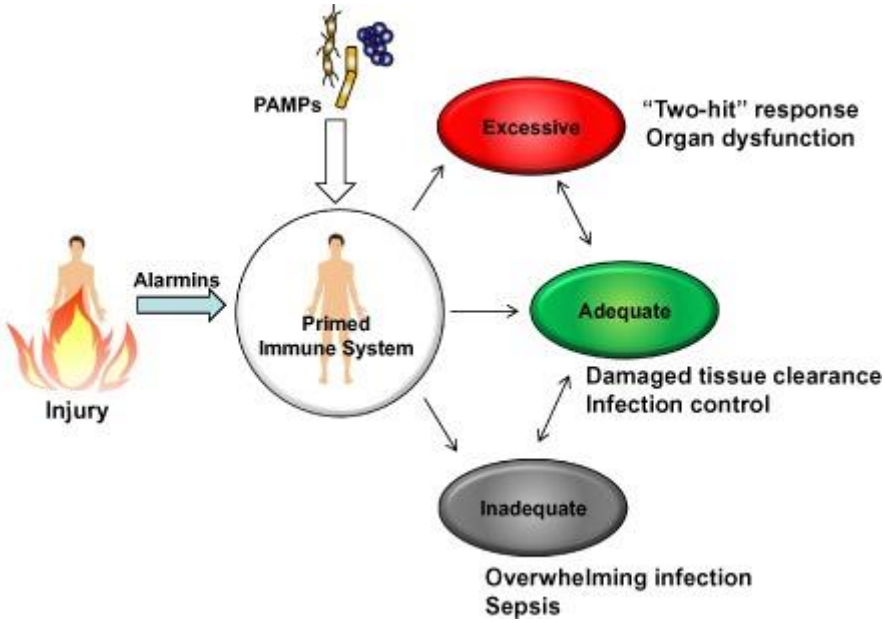

Figure 2

Injury primes the immune system. Following trauma, patients are exposed to alarmins that prime the immune system to defend against tissue injury and microbial invasion. This primed immune system can potentially trigger excessive inflammatory responses, which may lead to multiple organ failure. This excessive inflammatory reaction is known as the "two-hit" response. PAMPs, or pathogen-associated molecular patterns, play a role in this process.

Pro-inflammatory Responses to Trauma

Following traumatic injury, systemic inflammatory response syndrome (SIRS) commonly occurs. Our recent study found that injury activates the inflammasome pathway in lymph nodes draining the injury site within 2 hours, with this activation then spreading systemically. This activation mainly occurs in macrophages, as shown by caspase-1 activation. We also found that inhibiting inflammasome activation worsens outcomes post-injury. In mice with blocked inflammasome activation, cytokine profiles showed lower levels of interleukin (IL)-1β and significantly higher levels of IL-6. Clinical data suggest that patients who cannot develop a febrile response post-injury, which depends on IL-1β, have worse outcomes compared to those who do develop a fever. This difference may be due to variations in inflammasome activation pathways among patients.

Additionally, Paterson et al. demonstrated increased Toll-like receptor (TLR) reactivity in immune cells as early as one day post-injury, lasting for at least seven days, primarily in macrophages. Conversely, Zang et al. found that T cells exhibit pro-inflammatory activity shortly after injury, but this response decreases by day seven. By this time, T cells show a reduced pro-inflammatory phenotype and increased production of counter-inflammatory cytokines. Based on these findings, we propose that macrophages mainly drive the pro-inflammatory immune response following trauma, while T cells mediate the counter-

inflammatory response. Figure 3 illustrates the beneficial and detrimental phenotypes of inflammatory responses to injury.

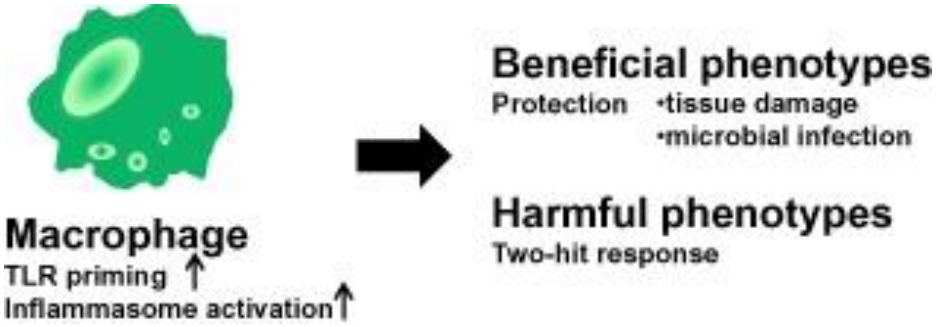

Figure 3 Inflammatory responses to injury are primarily driven by macrophages. Inflammasomes and Toll-like receptors (TLRs) are activated by alarmins. These inflammatory responses play vital roles in protecting the injured host by clearing damaged tissue and eliminating infections. However, excessive inflammation can lead to a two-hit response.

Beneficial Phenotype of Pro-Inflammatory Responses to Trauma

One theoretical explanation for the development of pro-inflammatory responses after trauma is their role in enhancing antimicrobial immunity to protect the host against secondary infections. Supporting this idea, Maung et al. demonstrated that trauma increases resistance to Escherichia coli infections, with resistance rising as early as one day post-injury and peaking at days 7 and 14. Similarly, Southard et al. found enhanced antimicrobial immunity in mice with a pulmonary contusion model. These findings highlight that the heightened reactivity of the innate immune system after trauma strengthens antimicrobial defenses. Clinically, this is supported by studies showing that patients with minor injuries often do not require antimicrobial treatments, suggesting that the mammalian immune system effectively protects against microbial invasions.

Detrimental Phenotype of Pro-Inflammatory Responses to Trauma

The concept of the "two-hit response" represents a notable complication following trauma. First coined by Moore et al., this phenomenon describes how initial traumatic injury sensitizes the body so that a subsequent minor inflammatory insult can trigger an exaggerated systemic inflammatory response. Recent studies highlighting increased Toll-like receptor (TLR) responsiveness post-trauma suggest that this two-hit response may stem from heightened TLR activity within the innate immune system, particularly in macrophages and neutrophils. These immune cells become overly responsive to bacterial stimuli and toxins, leading to heightened cytokine production. Consequently, this sequence can precipitate a secondary systemic inflammatory response resembling systemic inflammatory response syndrome (SIRS) and potentially multiple organ dysfunction syndrome (MODS).

Counter-Inflammatory Responses to Trauma

Counter-inflammatory responses are perceived as a natural compensatory mechanism in the host's reaction to inflammation induced by trauma, resembling a negative feedback signaling network within cells. Researchers have shown that severe injury reduces the body's resistance to infection through a response known as compensatory anti-inflammatory response syndrome (CARS). Evidence suggests that CARS is primarily orchestrated by the adaptive immune system, particularly T cells. This is supported by observations that severely

injured patients display weakened delayed-type hypersensitivity responses, prolonged survival of skin allografts, and decreased T cell proliferation in response to both general and specific recall antigen stimulation.

Additionally, trauma diminishes Th1-type immune responses while promoting Th2-type immune responses. For instance, Kelly et al. demonstrated that mice with burn injuries exhibited significant suppression of Th1 antibody responses and Th1-type cytokines in response to antigen immunization. Guo et al., using adoptive transfer methods, illustrated suppressed expansion of antigen-specific CD4 T cells and reduced production of Th1 cytokines without a concurrent increase in Th2-type responses. The potential beneficial and detrimental effects of T-cell-mediated counter-inflammatory responses to injury are summarized in Figure 4.

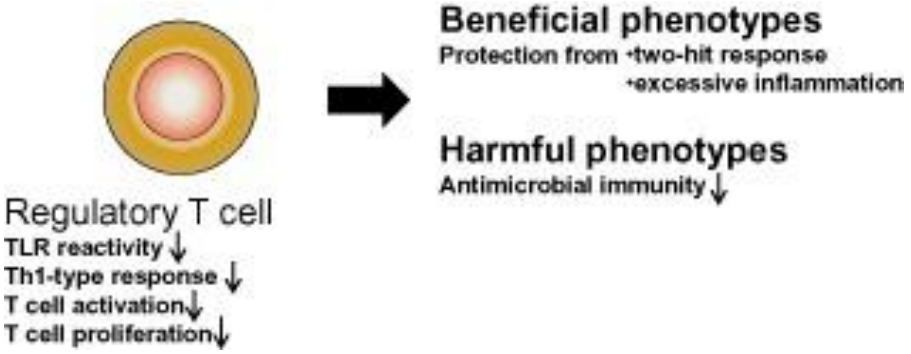

Figure 4

Counter-inflammatory responses following injury involve the activation of regulatory T cells, which regulate Toll-like receptor (TLR) reactivity and modulate T helper 1 (Th1)-type responses and T cell proliferation. This regulatory mechanism aims to safeguard the injured host from the adverse effects of the two-hit response and excessive inflammation. However, these counter-inflammatory responses may also increase the susceptibility of the injured host to opportunistic infections.

Beneficial Phenotype of Counter-Inflammatory Responses to Trauma

If the appearance of a counter-inflammatory response to injury represents a programmed or evolutionarily conserved immune system reaction, it deserves examination regarding its role in the context of trauma. One plausible rationale is that it functions as a mechanism to limit excessive inflammation following injury. Given our observations implicating T cells in orchestrating this response, our research has focused on investigating the role of a subset of CD4 T cells called regulatory T cells (Tregs). This focus arises from Tregs' well-established ability to modulate inflammation in autoimmune and inflammatory conditions, facilitated by their production of immune-suppressive factors such as transforming growth factor-β1 and IL-10.

Ni Choileain et al. demonstrated that Tregs derived from injured mice showed heightened effectiveness in inhibiting CD4 T cell proliferation compared to those from sham-operated mice. Additionally, they observed active suppression of Th1-type immune responses by Tregs in immunized mice. Furthermore, Hanschen et al. provided direct evidence of CD4+ Treg activation within 15 minutes post-burn injury in lymph nodes draining the injury site, suggesting a rapid and specific response of Tregs to tissue damage.

As previously mentioned, studies by Zang et al. revealed that intense T cell activation induced by bacterial superantigen injection shortly after trauma led to high mortality rates in mice. In contrast, no mortality occurred when injured mice were challenged with superantigen a week after injury, suggesting an in vivo shift towards a counter-inflammatory immune phenotype that may confer advantages. Clinically, these findings are significant as superantigens released by Gram-positive cocci could precipitate toxic shock syndrome in burn patients between 2 and 4 days post-injury. Given the timing of increased Treg numbers and their potent suppression of CD4 T cell activation, Treg activation might play a role in controlling toxic shock syndrome following injury.

Additionally, regulatory T cells may regulate innate inflammatory responses to trauma. Maung et al. found that Treg-deficient injured mice were significantly more susceptible to lipopolysaccharide challenge, with 100% mortality observed compared to 50% mortality in wild-type injured mice. These results suggest that Tregs actively modulate the severity of the two-hit response phenotype following trauma.

Harmful Phenotype of Counter-Inflammatory Responses to Trauma

One drawback of the counter-inflammatory response to injury lies in its potential to suppress antimicrobial immunity, which may contribute to the increased vulnerability of trauma patients to opportunistic infections commonly encountered during the counter-inflammatory phase of the injury response. While direct clinical correlations between post-injury sepsis development and altered Treg numbers or function have not been firmly established, evidence indicates that both injury and sepsis can impact Tregs in patients.

MacConmara et al. observed that circulating Tregs from trauma patients exhibit heightened activity within 5–7 days post-injury compared to Tregs isolated from patients in the early stages post-injury or from healthy individuals. Similarly, another study noted an increase in circulating Tregs among septic patients. These findings suggest that the increased presence or enhanced responsiveness of Tregs may be part of the host's response to sepsis and intense inflammatory reactions.

Further research efforts are needed to determine whether manipulating Tregs could potentially serve as a strategy to protect trauma patients from post-injury infections, sepsis, or systemic inflammatory complications.

Conclusions

The immune response to traumatic injuries represents a complex host reaction that undergoes evolutionary adaptations similar to other immune responses. Following injury, both innate and adaptive immune systems exhibit temporal changes characterized by distinct pro-inflammatory and counter-inflammatory phases. As depicted in Figure 5, the initial pro-inflammatory response to injury is primarily driven by the innate immune system, involving activation of inflammasomes and Toll-like receptors (TLRs), particularly in macrophages. In contrast, the subsequent counter-inflammatory response is predominantly governed by the adaptive immune system, notably through regulatory T cells (Tregs).

This review emphasizes that the immune response to injury follows a series of programmed reactions aimed at protecting the injured host from infections and excessive inflammation. Evidence indicates that localized infections can be effectively managed by the innate immune system. However, when injuries or infections evade control, broader immune

imbalances occur, disrupting immune system homeostasis (see Fig. 6). Restoring immune homeostasis is therefore proposed as a strategy to potentially prevent the development of opportunistic infections and systemic complications such as sepsis syndrome or organ failure.

Thus, advocating for future basic and pre-clinical research endeavors is crucial to deepen our understanding of how trauma disrupts immune system homeostasis. Moreover, developing therapeutic approaches aimed at restoring immune system balance holds promise in mitigating clinical complications among trauma patients.

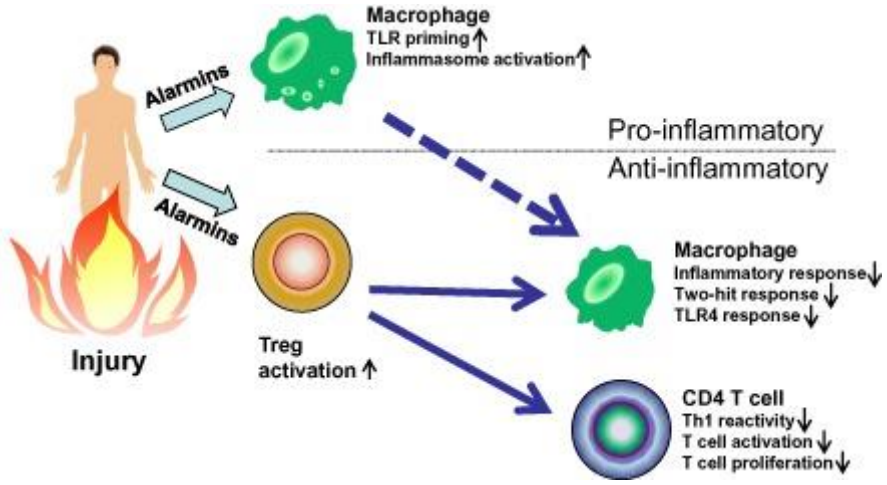

Figure 5

Interaction among immune cell subsets in response to injury involves a coordinated series of events. Tissue damage caused by injury releases alarmins, which activate macrophages and regulatory T cells (Tregs). In macrophages, injury induces several alterations in phenotype and function, such as heightened reactivity of Toll-like receptor 4 (TLR4) and increased antimicrobial responses. Meanwhile, Tregs are activated and play a pivotal role as "master regulators" of the injury response, exerting suppression over both innate (macrophage) and adaptive (T cell) cellular reactions to trauma.

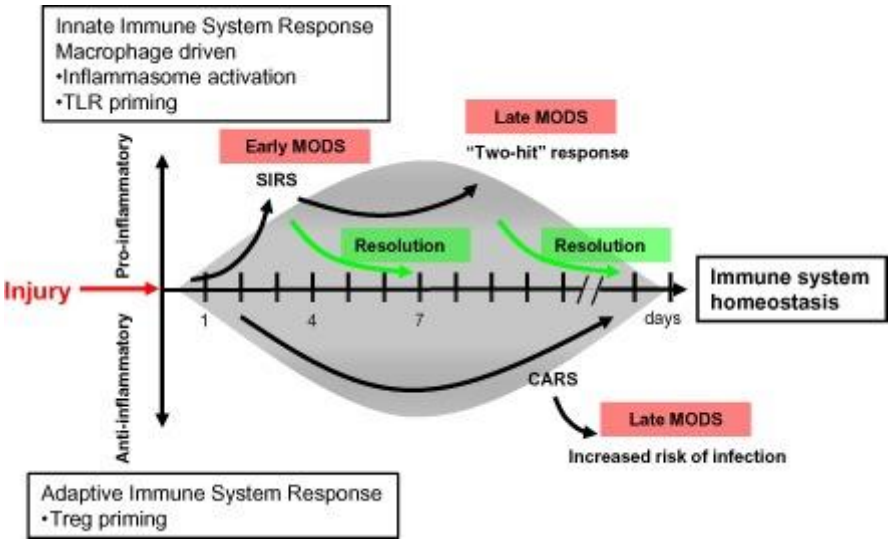

Figure 6

Traumatic injury disrupts the normal balance of the immune system, leading to systemic inflammatory response syndrome (SIRS) and compensatory anti-inflammatory response

syndrome (CARS) in trauma patients. The innate immune system drives the pro-inflammatory response, while the adaptive immune system regulates the anti-inflammatory response. Shortly after injury, inflammasomes are activated and Toll-like receptors (TLRs) are predominantly primed in macrophages. Simultaneously, regulatory T cells (Tregs) are also activated. An exaggerated pro-inflammatory phenotype can trigger the "two-hit" response, potentially resulting in multiple organ dysfunction syndrome (MODS). Conversely, an exaggerated counter-inflammatory response increases the risk of trauma-associated complications such as sepsis, septic shock, or MODS in the injured host.

References:

1. World Health Organization . The global burden of disease [database on the Internet]. 2013. [Cited 19 Aug 2013]. Available from URL: http://www.who.int/healthinfo/global_burden_disease/en/
2. Trunkey DD. Trauma. Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research. *Sci. Am.* 1983; 249: 28–35. [PubMed] [Google Scholar]
3. Wafaisade A, Lefering R, Bouillon B *et al* Epidemiology and risk factors of sepsis after multiple trauma: an analysis of 29,829 patients from the Trauma Registry of the German Society for Trauma Surgery. *Crit. Care Med.* 2011; 39: 621–628. [PubMed] [Google Scholar]
4. Moore FA, Moore EE, Read RA. Postinjury multiple organ failure: role of extrathoracic injury and sepsis in adult respiratory distress syndrome. *New Horiz.* 1993; 1: 538–549. [PubMed] [Google Scholar]
5. Baue AE, Durham R, Faist E. Systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), multiple organ failure (MOF): are we winning the battle? *Shock* 1998; 10: 79–89. [PubMed] [Google Scholar]
6. Baue AE. MOF, MODS, and SIRS: what is in a name or an acronym? *Shock* 2006; 26: 438–449. [PubMed] [Google Scholar]
7. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit. Care Med.* 1996; 24: 1125–1128. [PubMed] [Google Scholar]
8. 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: 1967–1974. [PubMed] [Google Scholar]
9. Matzinger P. The danger model: a renewed sense of self. *Science* 2002; 296: 301–305. [PubMed] [Google Scholar]
10. Harris HE, Raucci A. Alarmin(g) news about danger: workshop on innate danger signals and HMGB1. *EMBO Rep.* 2006; 7: 774–778. [PMC free article] [PubMed] [Google Scholar]
11. Oppenheim JJ, Yang D. Alarmins: chemotactic activators of immune responses. *Curr. Opin. Immunol.* 2005; 17: 359–365. [PubMed] [Google Scholar]
12. Manson J, Thiemermann C, Brohi K. Trauma alarmins as activators of damage-induced inflammation. *Br. J. Surg.* 2012; 99(Suppl. 1): 12–20. [PubMed] [Google Scholar]
13. Matzinger P. An innate sense of danger. *Ann. N. Y. Acad. Sci.* 2002; 961: 341–342. [PubMed] [Google Scholar]

14. Ogura H, Tanaka H, Koh T *et al* Priming, second-hit priming, and apoptosis in leukocytes from trauma patients. *J. Trauma* 1999; 46: 774–781, discussion 81–3. [PubMed] [Google Scholar]
15. Hoover L, Bochicchio GV, Napolitano LM *et al* Systemic inflammatory response syndrome and nosocomial infection in trauma. *J. Trauma* 2006; 61: 310–316, discussion 6–7. [PubMed] [Google Scholar]
16. Osuka A, Hanschen M, Stoecklein V, Lederer JA. A protective role for inflammasome activation following injury. *Shock* 2012; 37: 47–55. [PMC free article] [PubMed] [Google Scholar]
17. Mizushima Y, Ueno M, Idoguchi K, Ishikawa K, Matsuoka T. Fever in trauma patients: friend or foe? *J. Trauma* 2009; 67: 1062–1065. [PubMed] [Google Scholar]
18. Paterson HM, Murphy TJ, Purcell EJ *et al* Injury primes the innate immune system for enhanced Toll-like receptor reactivity. *J. Immunol.* 2003; 171: 1473–1483. [PubMed] [Google Scholar]
19. Zang Y, Dolan SM, Ni Choileain N *et al* Burn injury initiates a shift in superantigen-induced T cell responses and host survival. *J. Immunol.* 2004; 172: 4883–4892. [PubMed] [Google Scholar]
20. Maung AA, Fujimi S, MacConmara MP *et al* Injury enhances resistance to *Escherichia coli* infection by boosting innate immune system function. *J. Immunol.* 2008; 180: 2450–2458. [PubMed] [Google Scholar]
21. Southard R, Ghosh S, Hilliard J *et al* Pulmonary contusion is associated with toll-like receptor 4 upregulation and decreased susceptibility to pseudomonas pneumonia in a mouse model. *Shock* 2012; 7: 629–633. [PMC free article] [PubMed] [Google Scholar]
22. Grossman JA, Adams JP, Kunec J. Prophylactic antibiotics in simple hand lacerations. *JAMA* 1981; 245: 1055–1056. [PubMed] [Google Scholar]
23. Fan J, Li Y, Levy RM *et al* Hemorrhagic shock induces NAD(P)H oxidase activation in neutrophils: role of HMGB1-TLR4 signaling. *J. Immunol.* 2007; 178: 6573–6580. [PubMed] [Google Scholar]
24. Fan J, Kapus A, Li YH, Rizoli S, Marshall JC, Rotstein OD. Priming for enhanced alveolar fibrin deposition after hemorrhagic shock: role of tumor necrosis factor. *Am. J. Respir. Cell Mol. Biol.* 2000; 22: 412–421. [PubMed] [Google Scholar]
25. 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: 680–687. [PubMed] [Google Scholar]
26. Sauaia A, Moore FA, Moore EE, Lezotte DC. Early risk factors for postinjury multiple organ failure. *World J. Surg.* 1996; 20: 392–400. [PubMed] [Google Scholar]
27. Ninnemann JL, Fisher JC, Frank HA. Prolonged survival of human skin allografts following thermal injury. *Transplantation* 1978; 25: 69–72. [PubMed] [Google Scholar]
28. Lederer JA, Rodrick ML, Mannick JA. The effects of injury on the adaptive immune response. *Shock* 1999; 11: 153–159. [PubMed] [Google Scholar]
29. Faist E, Schinkel C, Zimmer S. Update on the mechanisms of immune suppression of injury and immune modulation. *World J. Surg.* 1996; 20: 454–459. [PubMed] [Google Scholar]

30. De AK, Kodys KM, Pellegrini J *et al* Induction of global anergy rather than inhibitory Th2 lymphokines mediates posttrauma T cell immunodepression. *Clin. Immunol.* 2000; 96: 52–66. [PubMed] [Google Scholar]
31. Kelly JL, O'Suilleabhain CB, Soberg CC, Mannick JA, Lederer JA. Severe injury triggers antigen-specific T-helper cell dysfunction. *Shock* 1999; 12: 39–45. [PubMed] [Google Scholar]
32. Murphy T, Paterson H, Rogers S, Mannick JA, Lederer JA. Use of intracellular cytokine staining and bacterial superantigen to document suppression of the adaptive immune system in injured patients. *Ann. Surg.* 2003; 238: 401–410, discussion 10–1. [PMC free article] [PubMed] [Google Scholar]
33. O'Sullivan ST, Lederer JA, Horgan AF, Chin DH, Mannick JA, Rodrick ML. Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. *Ann. Surg.* 1995; 222: 482–490, discussion 90–2. [PMC free article] [PubMed] [Google Scholar]
34. Mack VE, McCarter MD, Naama HA, Calvano SE, Daly JM. Candida infection following severe trauma exacerbates Th2 cytokines and increases mortality. *J. Surg. Res.* 1997; 69: 399–407. [PubMed] [Google Scholar]
35. Guo Z, Kavanagh E, Zang Y *et al* Burn injury promotes antigen-driven Th2-type responses in vivo. *J. Immunol.* 2003; 171: 3983–3990. [PubMed] [Google Scholar]