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Immunomodulation in transfused trauma patients

Rachael P. Jackman

Blood Systems Research Institute, San Francisco, CA

Abstract

Purpose of review—Traumatic injury is a major human health problem, with many injured people supported by transfusion of allogeneic blood. While trauma and transfusion have both been known to have immunomodulatory effects for some time, little is known about their combined effects or the scope and kinetics such responses.

Recent findings—Traumatic injury has a profound immunomodulatory effect on the patient, affecting a broad array of immunological components. This can be further complicated by transfusion, though the contribution of transfusion relative to the massive response triggered by trauma is small. The response to trauma involves a strong immunosuppressive component, which, contrary to the systemic inflammatory response syndrome/compensatory anti-inflammatory response syndrome model, occurs at the earliest time points examined and overlaps with pro-inflammatory and antimicrobial elements. This response is remarkably similar in a wide range of patients with different types and severities of injury.

Summary—The response to trauma and transfusion involves a massive and rapid reorganization of the immune system that can put the patient at increased risk of infection, tissue damage, and organ failure. The scope of the response presents challenges to the development of treatments to control this dysregulation.

Keywords

traumatic injury; transfusion; immunomodulation; inflammation

Introduction

Traumatic injury remains a critical challenge to human health. In the U.S., more than 2.8 million people are admitted annually for injuries, and traumatic injury is responsible for the majority of deaths between the ages of 1 and 44 years [1, 2]. Approximately 9% of trauma patients are transfused with a third of these given massive transfusions, and 9.1% of red blood cell units are utilized in the acute support of injured patients [3–5].

Traumatic injury has been known for some time to induce major immune dysregulation leaving patients vulnerable to both infection and exacerbated tissue damage. The dogma until recently was that the response to injury begins with a pro-inflammatory response termed the systemic inflammatory response syndrome (SIRS), and that this response triggers a later anti-inflammatory response termed the compensatory anti-inflammatory response syndrome (CARS) [6–8]. Each of these responses is thought to be useful in moderation, with mild inflammation needed as part of the normal healing process and gentle down-regulation

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Corresponding Author: Rachael P. Jackman, 270 Masonic Ave., San Francisco, CA, 94118, Phone: (415) 749-6606 ext. 714, Fax: (415) 567-5899, rjackman@bloodsystems.org.

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of this response needed to prevent excessive tissue damage, though a swing too far in either direction can result in multiple organ failure or systemic infection. Recent studies have shown, however, that this temporal separation between pro- and anti-inflammatory responses does not occur; instead, immunosuppression occurs early and simultaneously with select pro-inflammatory elements. This review will first give an overview of research on the immune responses to traumatic injury and allogeneic blood transfusion, and then discuss recent work on the magnitude, breadth, and kinetics of immune modulation following traumatic injury and blood transfusion.

Immune response to traumatic injury

Studies utilizing peripheral blood samples from human trauma patients have observed a number of changes in immunological parameters in the hours and days after injury. *Ex vivo* cellular assays have demonstrated altered T cell effector functions, an increase in regulatory T cell activity, and monocytes with decreased human leukocyte antigen (HLA)-DR expression and increased interleukin (IL)-10 and IL-6 production [9–16]. Circulating antibody levels shift, with increasing immunoglobulin (Ig)E and decreasing IgG [17–19]. A number of studies have also reported increases in circulating levels of IL-6, IL-10, IL-1Ra, and IL-8, with less consistent increases reported for tumor necrosis factor (TNF)- α and IL-4 [19–32]. A variety of murine models of trauma have been developed and have observed similar responses [33–41].

Immune response to transfusion

Blood transfusion is also immunomodulatory, having the potential for both activating and immunosuppressive properties, depending on the context. Transfusion is the most common form of transplantation and the introduction of allogeneic cells and soluble antigens frequently induces an alloimmune response [42–46]. This recipient response can drive a number of immunological sequelae including delayed hemolytic transfusion reactions, platelet refractoriness, and transplant rejection [44, 47, 48]. Immunologically active components of the transfused blood product, such as white blood cells, antibodies, cytokines, and microparticles can be immunomodulatory and have the potential to induce serious complications such as transfusion-associated acute lung injury and transfusion-associated graft-versus-host disease [49–54]. Immunosuppressive effects have been observed in some patient populations and animal models and have been shown to contribute potentially to both negative and positive clinical outcomes including increased susceptibility to infection and reduced renal allograft failure [55–61]. Finally, while rare in the developed world with modern blood-banking practices, transfusion-transmission of infectious agents can be pro-inflammatory and/or immunosuppressive, depending on the infection transmitted.

Studies on the combined effect of trauma and transfusion

Given the known immunomodulatory effects of both traumatic injury and allogeneic blood transfusion and the overlap between patient populations, there is a surprising paucity of studies assessing their combined effects on immune function. One interesting area of overlap is the study of transfusion-associated microchimerism (TA-MC), which appears to be unique to transfusion in the trauma setting. TA-MC is a phenomenon where donor cells persist in the recipient's circulation for months, years, or even decades after transfusion [62–70]. While the role of these cells is unknown, their persistence long after the patients have recovered from their injuries suggests that a unique immunosuppressive environment was in place at the time of transfusion. Murine models in which either burn or hemorrhage are combined with transfusion in anesthetized mice have found that the transfused mice had altered *ex vivo* cytokine profiles and natural killer cell activity, along with reduced resistance to infection when compared with control mice exposed to hemorrhage or burn alone [71–73].

Mechanisms regulating the immune response to trauma and transfusion

Traumatic injury and transfusion induce their immunomodulatory effects through a number of overlapping mechanisms driven by three primary sources: tissue damage, exposure to foreign antigens, and the stress/neuroendocrine response. These effects are further influenced by sex hormones.

Tissue damage—Damage to tissues, either directly from primary injury or as the result of surgical intervention, ischemia/reperfusion injury, or inflammatory responses, can induce immunomodulatory effects through the recognition of a category of innate immune activators called alarmins. Alarmins are endogenous molecules that are shielded from the immune system in healthy or apoptotic cells via localization in intracellular compartments, but can be released passively from necrotic cells, or actively from cells of the immune system to induce inflammation. These include several proteins such as high-mobility group box 1 protein and heat-shock proteins, as well as uric acid and mitochondrial DNA, and signal through a variety of receptors leading to NF- κ B activation [74–78]. Trauma patients can be susceptible to additional tissue damage induced from ischemia/reperfusion injury. Cerebrospinal fluid collected from patients after subarachnoid hemorrhage, for example, has been shown to have potent pro-inflammatory properties [79]. Murine models of high volume hemorrhage with or without resuscitation by autologous transfusion have demonstrated short-term defects in the production of IL-2 and proliferative capacity of splenocytes cells *ex vivo* [80–82]. Inflammation leads to additional tissue damage, resulting in a positive feedback loop.

Exposure to foreign antigens—While immune dysregulation following trauma decreases the body's ability to fight infection, the nature of the injuries inflicted and the procedures needed to treat them often increase the risk of exposure. Penetrating wounds, burns, and surgical interventions all disrupt epithelial barriers. Trauma can also result in increased endothelial permeability, leading to translocation of the intestinal microflora into the surrounding tissues and bloodstream [83, 84]. These exposures can lead to infection, but even in the absence of infection they can result in stimulation of innate immune responses by pathogen associated molecular patterns (PAMPs) found on pathogens and their components. Transfusion results in additional foreign exposures including allogeneic antigens, and in rare circumstances, infectious agents.

The stress/neuroendocrine response—The high levels of stress associated with traumatic injury can induce potent neurological and endocrine responses in the patient which contribute to the immunosuppressive response to trauma. The release of catecholamines as part of the fight-or-flight response leads to increased IL-10 production both *in vivo* and *ex vivo* and a reduced ability of patient cells to respond to lipopolysaccharide *ex vivo* [85–89]. The release of corticosteroids can lead to further immunosuppression [90–94].

Sex hormones—Sex hormones also impact immunological outcomes following trauma. Women have been found to have a reduced risk of death, sepsis, and multiple organ dysfunction syndrome as compared with men [95–99]. In murine models of trauma, disruption of the androgen/estrogen balance using a combination of castration/ovariectomy and administration of synthetic hormones demonstrates that androgens suppress responses to septic challenges, while estrogens enhance these responses [100, 101].

Recent advances

In the last 18 months, 2 key studies have looked broadly at the immune response to trauma and allogeneic blood transfusion. These studies challenge the previous paradigm of a primary SIRS response followed later by the CARS response, demonstrate the tremendous

scope of the immune response to traumatic injury, the additional role of blood transfusion to this response, and the conserved nature of this response.

The first study involved genome-wide expression analysis of RNA isolated from blood leukocytes collected from severe blunt injury patients (n=167), severe burn injury patients (n=133), healthy patients given a low dose of endotoxin (n=4), and healthy controls (n=37). These groups were compared with each other with additional comparisons made between 2 subsets of the blunt trauma cohort – those who recovered in less than 5 days (uncomplicated), and those who either did not recover until after 14 days, or died (complicated). The study focused on the first 4 weeks post-injury [102].

The second study focused on expression of soluble immune mediators in the blood of transfused (n=39) and non-transfused trauma (n=17) patients beginning with arrival in the emergency room, and following for 1 year after injury. A panel of 41 soluble immune mediators was assessed and expression patterns were modeled over time controlling for clinical parameters including the volume transfused. To identify the individual and combined contributions of traumatic blood loss and allogeneic blood transfusion on early immune modulation, a murine model was developed [103].

Scope of the immune response to traumatic injury—Xiao *et al.* found that of the 20,720 genes investigated, expression of 16,820 (>80%) were significantly altered in blood leukocytes following blunt trauma, appropriately naming this response a “genomic storm” [102]. Early responses involved an increase in the expression of genes regulating innate immunity, microbial recognition, and inflammation, but also anti-inflammatory mediators such as those involved with the IL-10 signaling pathway. Suppression of a number of genes was also observed as part of the early response, predominantly those involved in antigen presentation and T cell activation. Some upregulation of genes involved with B cell proliferation and immunoglobulin synthesis occurred later. Our study found a similar scope of response at the protein level, with levels of 31 out of 41 measured serum proteins significantly altered following trauma [103]. The early response was mixed, though predominantly anti-inflammatory with elevations in anti-inflammatory proteins such as IL-10 and IL-1Ra, and depressions in pro-inflammatory cytokines such as IL-1 α , IL-17 and TNF β . Some pro-inflammatory markers were elevated as well, such as macrophage migration inhibiting factor, as was the antimicrobial factor myeloperoxidase. A delayed elevation was seen in a number of proteins, predominantly those associated with wound healing, activated endothelial tissues, and lymphocyte homeostasis. Taken together, these studies demonstrate that the immune response to traumatic injury is incredibly broad in scope, with significant changes observed in a majority of the genes and proteins assessed.

Kinetics of the immune response to trauma/transfusion—In contrast with the SIRS/CARS model of inflammation after trauma, we now know that immunosuppression occurs immediately after injury, coincident with some pro-inflammatory elements. Most of the largest anti-inflammatory responses, at both the RNA and protein level, are seen at the earliest time-points examined. In the study from Xiao *et al.*, the first sample was collected within 12 hours post-injury, with cases fairly evenly distributed over the 12 hours. This was followed by frequent sampling in the first week, then weekly samples up to week 4. Our initial samples were collected at the time of admission (most within the first hour post-injury) and subjects were followed for up to 1 year, providing data after patients have recovered from their injuries. With the 1-year time-point used as the baseline, we observed 2 peak shifts in concentrations (Figure 1). The first peak shift occurred at the time of admission involving depression of many pro-inflammatory mediators, activation of anti-inflammatory mediators, and activation of some pro-inflammatory and anti-microbial mediators. This early response was mirrored in the mouse model, with similar cytokine

profiles seen at 4 hours after traumatic blood loss. The second peak change occurred 1–4 weeks out, and was dominated by increased levels of proteins involved in wound healing, lymphocyte homeostasis, and activated endothelial tissues. Xiao *et al.* found a similar clustering of events over time: a combination of up-regulation of genes involved in innate immune activation and immune suppression, and a depression of genes involved in adaptive immunity peaking at 12–24 hours, with a second cluster of expression shifts occurring between 1–4 weeks. Another recent study evaluated complement activity starting very early after trauma by collecting at the site of injury and continuing to collect frequently over the first 24 hours [104]. They saw peak loss of complement activity at 4 hours post-injury, although shifts in several components peaked at the scene, demonstrating how quickly the innate immune response is initiated.

The role of allogeneic blood transfusion—While the major immunological event for transfused trauma patients appears to be the injury, transfusion does influence this response. Xiao *et al.* found approximately 400 genes whose expression was dependent on the volume of blood transfused, most of which were down-regulated in response to transfusion [102]. We found that 7 of the 41 analytes measured were significantly different between patients receiving modest transfusions versus no transfusion when controlling for other clinical parameters such as injury type and severity. An additional 3 analytes were significantly higher among those receiving 5 units as compared with the modest transfusion group [103]. Though efforts were made in both of these studies to control for other variables that might be associated with transfusion, it is not possible to completely separate the effects of transfusion from the blood loss that necessitates it. To address this, we developed a mouse model of traumatic blood loss and allogeneic transfusion to distinguish the effects of traumatic blood loss and transfusion on the early immune response (4 hours post-injury). We found that transfusion exacerbated some cytokine responses, reversed some of the responses triggered by traumatic blood loss, and initiated some responses independently [103].

Conserved response to inflammatory stress—The response to traumatic injury is remarkably independent of the type or severity of injury, and has much in common with other responses to inflammatory stress. In our study, we were surprised to detect such a large number of significant changes in protein expression in response to trauma, especially with a relatively small cohort with diverse injuries [103]. When we examined the roll of injury-severity score (ISS) and blunt versus penetrating wounds while controlling for time since injury and other variables, we saw very few differences, and even our murine model induced similar cytokine expression patterns. Similarly, Xiao *et al.* found that no changes in gene expression were associated with ISS, only 8 were associated with base deficit in the first 12 hours, and that the direction of gene expression changes were the same for “complicated” patients and “uncomplicated” patients, though larger and more prolonged responses were seen in the complicated patients [102]. Strikingly, there were almost no differences in the early genomic changes associated with severe blunt trauma and burn injury (98% in the same direction), and remarkable overlap between blunt trauma patients and healthy endotoxin exposed controls (88% in the same direction).

Conclusion

The broad scope of the immune response to trauma along with the early and overlapping anti- and pro-inflammatory components has important implications for the management of patients and the development of new treatments. The similarities in the responses of patients with widely varying injuries suggest that there are common innate immune pathways driving this dysregulation. The breadth of this response presents challenges for the development of treatments targeting specific mediators, although a focus on early management of innate immune triggers holds some promise.

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Abbreviations

SIRS	Systemic Inflammatory Response Syndrome
CARS	Compensatory Anti-inflammatory Response Syndrome
IL	Interleukin
TNF	Tumor Necrosis Factor
PAMPs	Pathogen Associated Molecular Patterns
ISS	Injury Severity Score
TA-MC	transfusion-associated microchimerism
HLA	Human Leukocyte Antigen
Ig	Immunoglobulin

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Key points

- The immune response to traumatic injury is broad involving significant shifts in the expression of the majority of the leukocyte transcriptome and circulating soluble immune mediators.
- The immune response to traumatic injury involves an immediate immunosuppressive response that overlaps with pro-inflammatory elements, in contrast to the previous SIRS/CARS paradigm.
- The immune response to traumatic injury appears to have substantial overlap with a general inflammatory stress response and shows very few qualitative differences between patients with different injury types, severity, and outcomes.
- The role of allogeneic blood transfusion in modulating the response to trauma is significant, yet small relative to the massive changes induced by trauma.

Figure 1. Kinetics of immune response to trauma

Multivariable generalized estimating equations models were generated using the natural log of the concentration of each protein as the dependent variable and time since trauma, ISS, injury type, size of transfusion, age, sex, and microchimerism as the independent variables. Overlays of the models' predictions of the influence of time since trauma controlling for the other covariates are plotted by protein type. Predicted values at 1 year after trauma are set as the baseline (0) for each cytokine to show elevation or depression relative to this value. The inflammation plot includes the pro-inflammatory cytokines IL-1 α , IL-5, IL-9, IL-17, TNF α , TNF β , and macrophage migration inhibitory factor (solid lines), the anti-inflammatory cytokines IL-1Ra and IL-10 (dashed lines), and IL-6, which has both pro- and anti-inflammatory properties (dotted line). The healing plot includes the wound healing proteins epidermal growth factor, fibroblast growth factor 2, vascular endothelial growth factor, matrix metalloproteinase 9, and total plasminogen activator inhibitor 1 (solid lines), the activated endothelial markers soluble E-Selectin, soluble intercellular adhesion molecule 1, and soluble vascular cell adhesion protein 1 (dashed lines), and the homeostasis cytokines IL-7 and IL-15 (dotted lines). (Adapted from Jackman, R. P., et al. 2012, Transfusion. doi: 10.1111/j.1537-2995.2012.03618.x)