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Research review

Modeling acute traumatic injury

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ABSTRACT

Acute traumatic injury is a complex disease that has remained a leading cause of death, which affects all ages in our society. Direct mechanical insult to tissues may result in physiological and immunologic disturbances brought about by blood loss, coagulopathy, as well as ischemia and reperfusion insults. This inappropriate response leads to an abnormal release of endogenous mediators of inflammation that synergistically contribute to the incidence of morbidity and mortality. This aberrant activation and suppression of the immune system follows a bimodal pattern, wherein activation of the innate immune responses is followed by an anti-inflammatory response with suppression of the adaptive immunity, which can subsequently lead secondary insults and multiple organ dysfunction. Traumatic injury rodent and swine models have been used to describe many of the underlying pathologic mechanisms, which have led to an improved understanding of the morbidity and mortality associated with critically ill trauma patients. The enigmatic immunopathology of the human immunologic response after severe trauma, however, has never more been apparent and there grows a need for a clinically relevant animal model, which mimics this immune physiology to enhance the care of the most severely injured. This has necessitated preclinical studies in a more closely related model system, the nonhuman primate. In this review article, we summarize animal models of trauma that have provided insight into the clinical response and understanding of cellular mechanisms involved in the onset and progression of ischemia–reperfusion injury as well as describe future treatment options using immunomodulation-based strategies.

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1. Introduction

Acute traumatic injury has remained a leading cause of death affecting all ages in our modern society. According to the 2009 data from the National Trauma Institute, traumatic injury accounts for 30% of all life years lost in the United States as compared with 16% from cancer and 12% from heart diseases [1]. In the most recent Center for Disease Control and Prevention Data and Statistics report, of the 180,000 trauma-related deaths in 2010, most were attributed to hemorrhagic

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shock, central nervous system injury, and multiple organ failure (MOF) as sequelae of traumatic injury [2]. Direct mechanical tissue disruption and cellular damage coupled with physiological and immunologic disturbances brought about by acute blood loss, coagulopathy, ischemia–reperfusion injury (IRI) trigger dysregulated release and systemic accumulation of a cascade of proinflammatory cytokines and endogenous mediators of inflammation, which synergistically contribute to the increased incidence of post-injury morbidity and mortality as illustrated in the schematic in Figure 1. The pathogenic activation of the immune system manifests itself in a bimodal pattern, wherein the trauma activates and/or primes the innate immune system as characterized by an initial proinflammatory systemic surge (systemic inflammatory response syndrome [SIRS]) and is subsequently followed by suppression of the adaptive immunity (compensatory anti-inflammatory response syndrome [CARS]). Patients who survive the "first hits" of a trauma (acute blood loss and/or hypotension, hypoxia, and soft tissue injuries, fractures) in this primed and immunosuppressed state are susceptible to "secondary hits," such as infections, IRI, and/or the stress of surgical interventions, which can ultimately lead to multiple organ dysfunction syndrome (MODS) [3–6]. Therefore, MODS is attributed to the cumulative insults on the body rather than on one event [7].

Numerous traumatic injury studies using animal models have described the underlying mechanisms and elucidated primary and secondary sequelae that contribute to the understanding of morbidity and mortality of the critically ill trauma patient [8–10]. Conversely, the enigmatic immunopathology of the human immunologic responses after severe traumatic injury has never more been apparent. As our understanding and ability to manipulate the molecular and cellular components involved in this maladaptive immune response develops, the inherent limitations of existing animal models become apparent and there grows a need for clinically relevant animal models, which mimic this immunophysiology. An advanced large animal model will allow for the development of new and more effective management and treatments options to enhance the care of the most severely injured.

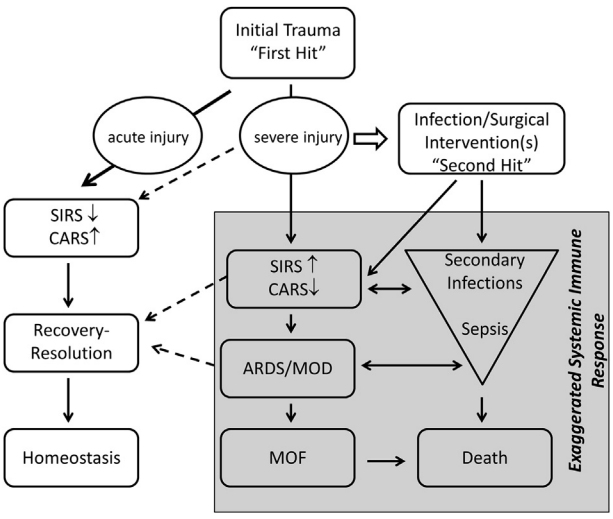

Fig. 1 – Systemic activation of the immune system after traumatic injury stimulated by primary and secondary insults ("two hit" model). CARS = compensatory anti-inflammatory response syndrome; MOD = multiple organ dysfunction; SIRS = systemic inflammatory response syndrome.

This review will explore the known immunophysiology of trauma and investigate the different experimental animal models of acute traumatic injury that have provided insight into the clinical response and understanding of cellular mechanisms involved in the onset and progression of hemorrhage, tissue injury, and IRI. Moreover, we review the current trauma research, which uses immunomodulation-based treatment strategies to mitigate the immune response in animal trauma models in an effort to improve clinical outcomes after severe injury.

1.1. *The immune response to trauma and injury*

The human body's response to injury is undeniably a multifaceted array of complex and overlapping phases of cellular and molecular events purposed to promote wound healing and reestablish homeostasis. A variety of clinical studies and experimental animal models have been used to evaluate these mechanisms. The association between tissue injury and/or repair and inflammation has long been established. The inflammatory response orchestrates host defenses to combat microorganisms and mediate tissue repair and regeneration [11,12]. Locally, early wound healing consists of a microenvironment milieu containing a dynamic network of resident and infiltrating inflammatory cells integrated within a multitude of soluble mediators with pleiotropic, redundant, and opposing effects. The balance of these interactions is thought to determine wound-healing outcomes [13,14].

Beyond local wound healing, severe traumatic injury can induce immunologic dysfunction often characterized as an altered state of host defense [15]. This altered state is regarded as an early overactivation of the innate immune response followed by an exuberant anti-inflammatory response causing suppression of the adaptive immunity with decreased T cell function [16,17]. The systemic consequences of this inflammatory response can compromise clinical outcomes. Nuytinck *et al.* [18] reviewed autopsy specimens of 35 trauma patients who died 24 h or more after injury. Histologic analysis of tissues collected postmortem showed signs of marked systemic inflammation, such as neutrophil accumulation, interstitial, and cellular edema [18]. Similar evidence of systemic inflammation and neutrophil infiltration has been demonstrated in multiple animal models, which induce shock from trauma including the physiologic liver hemorrhage swine model developed in our laboratory [19].

The etiology of this systemic inflammation is in part explained by the Danger Theory [20], as seen in Figure 2, which describes the inflammatory reactions after injury. This response can be provoked by the secretion, activation, or passive release of endogenous "danger" and/or alarm signals ("alarmins") by the injured cells and/or necrotic cells in response to tissue damage and/or infection. These alarm signals are generally categorized as damage-associated molecular patterns (DAMPs), which bind to toll-like receptors [5,21]. These factors not only function as potent activators of