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Role of biological modifiers regulating the immune response after trauma

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Summary Trauma induces a profound immunological dysfunction. This is characterised by an early state of hyperinflammation, followed by a phase of immunosuppression with increased susceptibility to infection and multiple organ failure. Therapeutic strategies directed at restoring immune homeostasis after traumatic injuries have largely failed in translation from ''bench to bedside''. The present review illustrates the role of biological modifiers of the posttraumatic immune response by portraying different modalities of therapeutic immune modulation. The emphasis is placed on anti-inflammatory (steroids) and immune-stimulatory (interferon) pharmacological strategies and modified resuscitative strategies, as well as more unconventional immunomodulatory approaches, such as immunonutrition.

Introduction

Severe trauma is associated with altered host defence, characterised by an early over-activation of innate immune responses (hyperinflammation), followed by a delayed attenuation of adaptive immunity with decreased T-cell function (immunosuppression) and enhanced susceptibility to infection, sepsis, and multiple organ failure.[10,65,74,87,96,180] During both phases of hyper- (''systemic inflammatory response syndrome'', SIRS) and hypo-inflammation (''compensatory anti-inflammatory response syndrome'', CARS), injured patients are highly susceptible to ''2nd hits'' which exacerbate the pathophysiological cascade leading to sepsis, multiple organ failure, and death.[10,87,116] The objectives of immunomodulatory therapies are aimed at attenuating the detrimental side-effects of the early hyperinflammatory cascade and preventing additional insults which can provoke the inflammatory host response into a ''host response failure disease'' with adverse outcome. Concomitantly, the cell-mediated, adaptive immune response must be supported to overcome the

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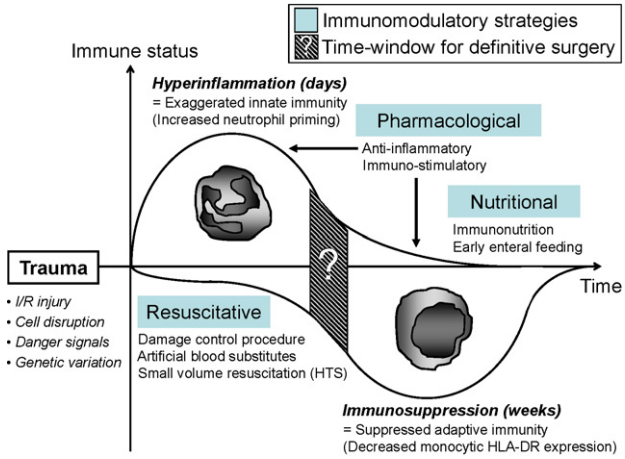

Figure 1 Immune response phases after trauma and immunomodulatory targeting options. During the phases of hyperinflammation and immunosuppression, severely injured patients are highly susceptible to sustain so-called "2nd hit" insults. Thus, the ideal timing for definitive surgery lays somewhere between these two "extreme" immunological phases. While the suggested time-window of opportunity has been empirically assigned to about 5—10 days after trauma, clear-cut data from evidence-based research is still lacking to answer this question conclusively. HTS, hypertonic saline; HLA-DR, human leukocyte antigen-DR; I/R, ischaemia/reperfusion.

delayed posttraumatic functional immune paralysis (Fig. 1).

Inflammatory response to trauma

Innate immunity

The innate immune response is crucial as an immediate "first line of defence" against antigens recognised as non-self entities. These include infectious agents, such as viruses, bacteria, and parasites, as well as host-generated dangers, such as malignant tumours. A traumatic impact is also capable of inducing an activation of innate immune responses.[66,74,131,141,159] The trauma-induced immune response may be limited locally, as in mono-trauma, or result in a massive systemic immune activation (SIRS), as in polytrauma.[10,42,87,142] The endogenous triggers of trauma-associated inflammation have been thoroughly investigated and characterised in recent years.[74,87,141,143,180] Among these, the complement system appears to represent the "key" mediator of innate immune responses after trauma.[30,49,98,109] Once activated through one of three established pathways, complement plays a critical role in the elimination of invading pathogens by opsonisation for phagocytosis (C3b, C4b), chemotaxis of leukocytes (C3a, C5a), and by direct lysis of pathogens through the membrane attack complex (MAC, C5b-9).[37,40,99,109] The anaphylatoxins C3a and C5a are potent chemoattractants for phagocytes and polymorphonuclear leukocytes (PMNL, "neutrophils"), and recruit these immune cells to the site of injury.[62] The anaphylatoxins further induce degranulation of mast cells, basophils and eosinophils and mediate the hepatic acute-phase response.[40,99,109] Finally, the generation of C5b by cleavage of C5 initiates the terminal complement pathway with MAC formation. The MAC forms through the self-association of C5b along with C6 to C9 and leads to the formation of a large membranolytic complex capable of lysing prokaryotic and eukaryotic cells.[40,99,109] Clinical and experimental studies have demonstrated that complement activation occurs both locally, at the site of injury, as well as systemically after trauma.[11,55,66,68,159,160] The systemic activation of the complement cascade has been shown at the level of C3 in serum of trauma patients, and the extent of activation was correlated to the severity of injury.[85,86,131,148]

Danger signals: PAMPs, DAMPs, and alarmins

"Pathogen-associated molecular patterns" (PAMPs) represent a heterogenic entity of recently described inflammatory molecules related to the innate immune system.[50,81] These microbial molecules are recognised by the immune system as foreign due to their characteristic molecular patterns. In contrast, the so-called "alarmins" represent the correlate of PAMPs for all non-pathogen-derived danger signals which originate from tissue injury.[14] These include heat-shock proteins (HSPs), annexins, defensins, as well as "classical" markers of tissue injury, such as the S100 protein and the high mobility group box 1 (HMGB1) nuclear protein.[14] These alarmins are endogenous molecules capable of activating innate immune responses as a signal of tissue damage and cell injury. Together, PAMPs and alarmins have been recently suggested to form the larger family of "damage-associated molecular patterns" (DAMPs).[14] Immune cells recognise both PAMPs and DAMPs through multiligand receptors, such as Toll-like receptors (TLRs), expressed on their surfaces.[180] Thus, DAMPs represents a newly recognised large superfamily of danger signals which can activate innate immune responses after trauma, both as a result of injury alone (alarmins) and in the case of trauma-related infectious complications, such as sepsis. The list of molecules related to the DAMP family has just been emerging and their pathophysiological function in trauma-induced inflammation is still far from being fully understood.[14,180]