Review Articles

Immunology of Septic Shock and Traumatic Injury: A Review

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Abstract: Sepsis remains a major worldwide cause of morbidity and mortality and remains amongst the leading causes of death in medical Intensive Care Units (ICUs). Increasing injury severity associated with trauma is a significant independent risk factor for sepsis and many of these patients require intensive care unit resource utilization with increased rates of mortality. There are many postulated theories regarding the mechanism surrounding the correlation between trauma and shock. One such theory evaluated the deterioration of the immune system after trauma with the activation of Damage Associated Molecular Proteins (DAMPs) and the potential role of mitochondrial release into the bloodstream following physical injury leading to the onset of the Systemic Inflammatory Response Syndrome (SIRS). Despite these proposed theories, a breach of cellular integrity seems to unravel a multitude of immunologic responses that in essence account for the deleterious symptoms associated with sepsis. The association between traumatic injury and sepsis is very complex. This review explores the multifaceted immunoinflammatory response and gives an in depth immunologic explanation of the fundamental mediators in the initiation and continuation of the inflammatory response following the loss of cellular integrity.

Keywords: Sepsis, Trauma, Injury, SIRS, Procalcitonin

Introduction

Background

Post-traumatic sepsis is a significant cause of mortality and there are many factors, both demographically including age and race and injury factors including the mechanism and severity of injury that predict post traumatic sepsis to a considerable extent (Osborn *et al.*, 2004). Worldwide, in the general population under the age of 45, trauma is one of the main causes of death (Wafaisade *et al.*, 2011). Although there are many immediate effects of trauma following the initial injury including cellular hypoxia and/or severe hypovolemic shock secondary to bleeding, traumatic injury leads to an immunologic deterioration in those individuals that survive. All severe posttraumatic complications including SIRS, Acute Respiratory Distress Syndrome (ARDs) and Multiple Organ Dysfunction (MODS) are directly related to synthesis and release of inflammatory mediators into the bloodstream. Trauma can induce immune function

changes known as Systemic Inflammation Response Syndrome (SIRS) and immunosuppression as Compensatory Anti-inflammatory Response Syndrome (CARS). SIRS with a known or predicted source of infection is referred to as sepsis. Due to the fact that it is difficult to isolate the microbial inoculums the differential diagnosis between SIRS and sepsis is unclear to many health care professionals. Clinically it is difficult to isolate the microbial inoculums thus making the differential diagnosis between SIRS and sepsis difficult. In multiple trauma situations, both syndromes can develop simultaneously, recently described as Mixed Antagonist Response Syndrome (MARS) (Novotny, 2010). A recent review covered sepsis and the systemic immune response, the role of cytokines and Procalcitonin (PCT), role of steroids in sepsis, innate immunity and reactive oxygen species related to sepsis and the impact on neutrophil function. PCT has been proven to be a superior biomarker for sepsis diagnosis and for the prediction of its clinical outcome. In addition to the standard clinical workup of a patient, including

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history, physical exam and laboratory findings, the use of PCT has many clinical implications in sepsis that can help streamline the potential diagnosis and rule out other differential diagnoses. It is clear that there are several benefits of integrating the use of PCT into practice in the early golden hours of sepsis diagnosis and can undeniably help prescribers treat the patient both more appropriately and efficiently (Frieri *et al*., 2015a). Although there are many foreseen benefits of PCT integration into the clinical practice there is still a need for better understanding for the role of PCT and its correlation to the immune response. Further clinical trials that explor immunological role of PCT in sepsis are needed to confirm its sensitivity and sensitivity in the sepsis clinical picture.

The body's first line of defense, the epithelial barrier, is often disrupted in trauma allowing for the penetration of microorganisms into the blood stream and a prolonged state of immune-inflammatory dysregulation. SIRS which is manifested by an excessive proinflammatory response due to the immediate blunt trauma is initiated by the innate immune response. This is then followed by a compensatory anti-inflammatory response syndrome which essentially suppresses the adaptive immune response allowing for bacteria to thrive and infiltrate the host's immune system (Thornhill *et al*., 2010). The combination of a dampened immune response and a hyperinflammatory state mediated by traumatic injury significantly increases the risk for developing acquired infectious complications.

The Role of the Immune System Following Traumatic Shock

The Role of the Mitochondrion in Trauma and Shock-A Non Infectious Cause of SIRS?

As "power plants" of eukaryotic cells, providing energy in the form high energy phosphate bonds of ATP, mitochondria are theorized to be from bacterial origin and exist in eukaryotic cells in an endosymbiotic relationship. Due to their close resemblance to the bacteria from which they originated mitochondria appear to elicit a sepsis-like response characteristic of releasing Damage-Associated Molecular Patterns (DAMPS) (BIDMC, 2010). With direct insult from traumatic injury, SIRS causes many of the vital organs to become dysfunctional as a direct consequence of inflammation. The innate immune response that is present from birth remains the focal point that underlie both SIRS and sepsis, activating Pathogen Associated Molecular Patterns (PAMPs) (BIDMC, 2010). These PAMPs activate a group of cellular responses jointly known as the 'Danger Response' that is present in both sepsis and traumatic injury. Trauma associated with blunt force can result in the death of considerable amounts of tissue activating a very similar immune response that is seen with the body's response to external pathogens such as bacteria or viruses. In the presence of trauma normally intra cellular molecules, like mitochondria, can activate Pattern Recognition Receptor molecules (PRR), at which point they become DAMPs. A recent paper published by Watts hypothesized that DAMPs and PAMPs have many similar mechanisms for triggering inflammation in both the setting of trauma and infection and, mitochondria may in fact be ultimately responsible for inflammation in both cases (Watts and Kline, 2003). Due to mitochondria's autonomous functional capacity and their own DNA, which is a completely separate and distinct entity from the genetic material contained within the cell's nucleus, mitochondria in fact share many similarities with bacteria. Both bacteria and mitochondria share similarities in their method of reproduction, the molecular nature of their DNA and their synthesis of n-formylated proteins (BIDMC, 2010; Watts and Kline, 2003). Based on the similarity between mitochondria and bacteria it is plausible to hypothesize that mitochondria can induce a pro inflammatory state with the release of DAMPs into the circulatory system, in the same way that infections do when they release PAMPs following mechanical trauma. Following traumatic or physical injury mitochondria are released into the bloodstream and the fact that they resemble many of the features of bacteria mentioned previously, mitochondria can elicit an immune response very similarly to the way bacteria elicit an immune response in sepsis. Mitochondria which spill into the bloodstream following a physical injury look enough like the bacteria they originated from to elicit an immune response and mirror that of bacterial sepsis. The fact that tissue death caused by traumatic injury has just as much potential for causing SIRS as does infection, treatment modalities aimed at blunting the hyperinflammatory state may arise in the near future with continued research. The plasma membrane, endoplasmic reticulum, Golgi apparatus and the mitochondria are responsible for many of the exceedingly regulated redox reactions of aerobic metabolism and of equal importance are quinones which essentially are electron and proton carriers that play a primary role in the aerobic metabolism of practically every cell in nature. Although these redox reactions produce a significant amount of the energy the body needs to sustain life, these electron transfer reactions also consequently produce Reactive Oxygen Species (ROS) that play important roles in damage to the body at a molecular level (Madeo *et al*., 2013). Review of the literature, revealed evidence of significant correlations between production of ROS and inflammatory responses in an exponential relationship, as the

production of ROS increases the greater the inflammatory response is. The underlying mechanisms by which the inflammatory response and ROS production occur was also be discussed (Madeo *et al*., 2013; Saad *et al*., 2013).

The role of mitochondria in initiating apoptosis and activating danger signals is well known in the literature. With blunt trauma and tissue cell injury mitochondria become hyperpolarized and the transmembrane potential becomes uncoupled and irreversibly damaged and Reactive Oxygen Species (ROS) production significantly increases as a result of diminishing ATP production, leading inevitably toward irreversible cellular damage via apoptotic mechanisms (Watts and Kline, 2003). The transient opening of pores during this cellular injury leads to the development of mitochondrial component proteins into the cytoplasmic space activating a vicious cycle of danger signals as depicted in Fig. 1.

Mitochondria also produce ROS as a result of cellular hypoxia which effectively induces oxidative damage on both the mitochondrial DNA and proteins residing in the mitochondria. Under normal physiologic conditions our body is able to effectively scavenge these ROS via endogenous antioxidants, however, under conditions of oxidative stress as seen in trauma, the host defensive mechanisms become overwhelmed as a result of the increasing ROS levels and irreversible mitochondrial damage ensues, consequently leading to organelle dysfunction and ultimately cell death (BIDMC, 2010). It is clear that mitochondria play a major role in the physiological response to trauma and shock and often mitochondrial function becomes depressed and eventually dysfunctional with severe insult. As tissue injury generates a state of hypoxia, deranged metabolism of the mitochondria can lead to significant ROS production, which can potentially to damage cellular integrity including cellular protein production and damage to the host host's genomic DNA.

Deterioration of the Immune System after Trauma

The Injury Severity Score (ISS) and the Acute Physiology And Chronic Health Evaluation (APACHE II) scores help stratify patients based on the severity and extent of traumatic injuries (Flohe *et al*., 2008). The ISS and APACHE are widely used and remain the gold standard for prediction of multi-organ failure and development of septic complications. As a general statement, patients with higher scores in both of the ISS and APACHE have a higher mortality rate due to multi-organ failure and statistically develop higher rates of septic complications (Flohe *et al*., 2008). Hyperinflammation following traumatic injury mediates remote end organ damage and may lead to multi-organ failure; In addition immunosuppression secondary to insult of the epithelial barrier promotes an increased risk to acquire infectious complications.
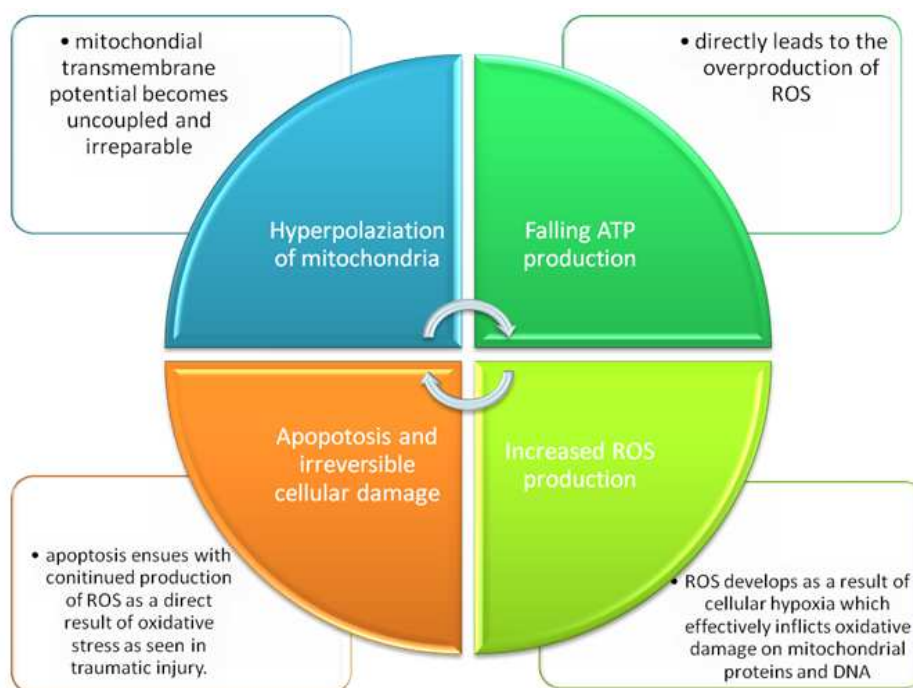

Fig. 1. Vicious cycle of danger signals as a result of leaking mitochondrial components

How in fact these mechanisms of hyperinflammation and immunosuppression develop are poorly understood however there is developing evidence that damaged tissues which release endogenous danger signals play a developing role in the immune dysfunction seen in traumatic injury (Marshall, 1997). Shock associated with trauma is often associated with major bleeding leading to hypovolemia however the trauma induced disturbance in the host's immune system cannot be solely reduced to the response of hypovolemic shock. A secondary mechanism of autonomic and pathologic dysfunction must account for the trauma-induced modulation of the immune system. Many animal studies have been performed that have aimed to investigate the deterioration of the innate and adaptive immune system following traumatic injury. A study performed by German investigators in 2008 concluded that the initiation of a 'cytokine storm following a hyper-inflammatory state in addition to other immunologic mediators including' activation of macrophages and granulocytes results and macrophages result in end organ damage. Also theorized in this study was that down-regulation and dysfunction of Antigen-Presenting Cells (APCs) and T-cells, in an immunosupressed state leads to greater risk of attaining infectious complications. Ultimately endogenous danger signals released following traumatic injury were hypothesized to be subsequently involved in both processes (Flohe *et al.*, 2008; Marshall, 1997; Cavaillon and Annane, 2006).

Severe trauma, irrespective of mechanism, commonly causes substantial amounts of blood loss leading to decreased endothelial derived Nitric Oxide (NO), which further leads to augmented platelet aggregation, increased neutrophil infiltration and deregulation of vasorelaxation (Surbatovic *et al.*, 2013). As expected with trauma, loss of endothelial integrity increases vascular permeability, characteristic of the innate immune response reacting to DAMPs. Adaptive immune response is not seen in the initial reaction to trauma as antigen-specific reaction requires more time (Lenz *et al.*, 2007). Antigen presenting cells, such as monocytes and macrophages, effectively recognize the foreign invading pathogen and through uptake into the cytoplasm and lysosome often times are able to kill the microorganism. In septic complications following severe trauma often times monocyte function is impaired further rendering the antigen-presenting capabilities ineffective. Nitric Oxide (NO) and Tumor Necrosis Factor Alpha (TNF-alpha), a pleiotropic inflammatory cytokine, are activated upon epithelial injury which stimulate pro-apototic signaling proteins of immune effector cells, which may contribute to sepsis-associated MODS after severe trauma (Lenz *et al.*, 2007). In addition downstream activation of neurohormal mechanism of

catecholamine's and glucocorticoids binding to their corresponding receptors on immune cells also suppress cytokine production and thus impair a competent immune regulatory cell-cell interaction (Tschoeke and Ertel, 2007).

Site targeted complement inhibition is a new pathophysiological pattern that looks at both the beneficial and detrimental role of complement following trauma (Neher *et al.*, 2011). A review on complement considered some basic aspects of complement biology, addressed the clinical effects of hereditary compliment deficiencies as well as the role of compliment related to host cell entry, pathogenesis of infectious diseases and apoptosis. This immunomodulation of autoimmune and inflammatory disorders related to complement components, mechanisms of autoimmune urticaria and tolerance was also discussed (Frieri, 2002). Complement plays a major role in sepsis mediating the activation of the innate immune response however this activation can also contribute to the pathogenesis of trauma induced sequelae and adverse outcome. Complement is able to effectively eliminate pathogens and respond to danger signals exerting its beneficial effect; despite this seeming advantageous effect, complement activation may exert detrimental effects following traumatic injury on host tissue. By mounting an immune response on "innocent" tissue, complement activation is causing more harm than good and damaging viable tissue by exacerbating local and systemic inflammation, thus adding to the antigenic load. The combination of hyperinflammation and exacerbation of toxic mediators consequently sustain SIRS after major trauma and ultimately contributing to remote organ injury and death (Morris *et al.*, 2013).

Endogenous signals such as HMGB-1 and Heat Shock Proteins (HSPs) upon binding to their corresponding receptors (i.e., TLR4) activate macrophage cytokine release in damaged tissue (McGhan and Jaroszewski, 2012). This cascade essentially mediates trauma-induced immune dysfunction through propagation of the inflammatory response following disruption of cellular integrity. It is clear that there are several factors that contribute to the immune response and end organ damage after trauma. The imbalance between a hyperinflammatory state and attenuated immune response contribute to the septic complications following traumatic injury.

Danger Signals Activating the Immune Response after Trauma: HMGB-1, IL-1a, IL-33

DAMPs, also known as alarmins, are endogenous danger signals that are released from necrotic or stressed cells that effectively initiate the inflammatory response following trauma. There are 3 main alarmins that are central to the inflammatory response including High

Mobility Group Box Protein 1 (HMGB -1), interleukin 33 (IL-33) and Interleukin-1 alpha (IL-1a) as depicted in Fig. 2. There are other alarmins including galectins, adenosine and thioredoxin that play a role in signaling downstream inflammatory activation however, HMGB-1, IL-33 and IL-1a have unique dual-function mediator properties in the initiation of the immune response after trauma that is most concerning to us as practitioners (Hirsiger *et al*., 2012). A study was done which compared healthy volunteers to pre-oesophagectomy patients, patients with SIRS and/or sepsis and neutropenic patients with sepsis and looked at levels of Thioredoxin (Trx), macrophage Migration Inhibitory Factor (MIF), IL-6, IL-8, IL-10 and Procalcitonin. As expected, plasma levels of these mediators were significantly more prevalent in patients with SIRS/sepsis. A subset analysis was done that compared the different mediators and suggested a unique correlation between that of Trx and MIF. The investigators found that both Trx and MIF were substantially lower in patients in the group of patients with neutropenia compared with those patients enrolled in the SIRS/sepsis group (Leaver *et al*., 2010). This relationship is noteworthy and further studies are needed to elucidate the implications of this correlation in septic shock associated with traumatic injury.

Alarmins are pro-inflammatory mediators of the immune system and contribute to the activation of a mixture of immune cells including Mast Cells (MC's) and macrophages during infection and tissue damage (Basu *et al*., 2000). These activated MCs go on to release pro-inflammatory mediators including histamine and several proteases. Although MCs may play a role in the perpetuation of the immune response, they are able to degrade alarmins via a chymase-specific mechanism that has been suggested to serve as a protective and regulatory role. The MC chymase specific degradation of

alarmin specific Heat Shock Protein (HSP70), HMGB1, IL-33 and biglycan, may limit danger induced inflammation however this is not fully understood (Scaffidi *et al*., 2002). It is important to understand that alarmins are released during injury and include the High Mobility Group Protein B1 (HMGB1) and cytokines of the IL-1 family, such as IL-1α, IL-18 and IL-33 as mentioned previously (Chen *et al*., 2007; Yang *et al*., 2007; Moussion *et al*., 2008; Schmitz *et al*., 2005). A recent review how trauma can involve a variety of triggers and mechanistic areas related to the various roles of mast cells in trauma, mediators, cytokines and neuroinflammation that play important roles in allergic and immune disorders was published (Frieri *et al*., 2015b).

Role of HMGB-1

Sterile injury, which encompasses hemorrhagic shock and ischemia/reperfusion injury induces the release of many inflammatory cytokines however the focus of this section involves the release of HMGB1, a proinflammatory cytokine released by many cells of the immune system (Tsung *et al*., 2005). As an inflammatory mediator, HMGB1 exerts pleiotropic proinflammatory effects on various organ systems mainly through its ability to activate phagocytic and endothelial cells that promote tissue repair, chemotaxis, angiogenesis and recruitment and proliferation of stem cells (Wang *et al*., 2004). The activities of HMGB-1 are all mediated through its interaction with pathogen-recognition receptors and Toll Like Receptors (TLRs), which also recognize products from invading microorganisms. In addition, the concentration of HMGB-1 correlate with the severity of injury and the systemic inflammatory response, acting as an early proinflammatory mediator peaking from 2 to 6 hours following traumatic injury (Klune *et al*., 2008).
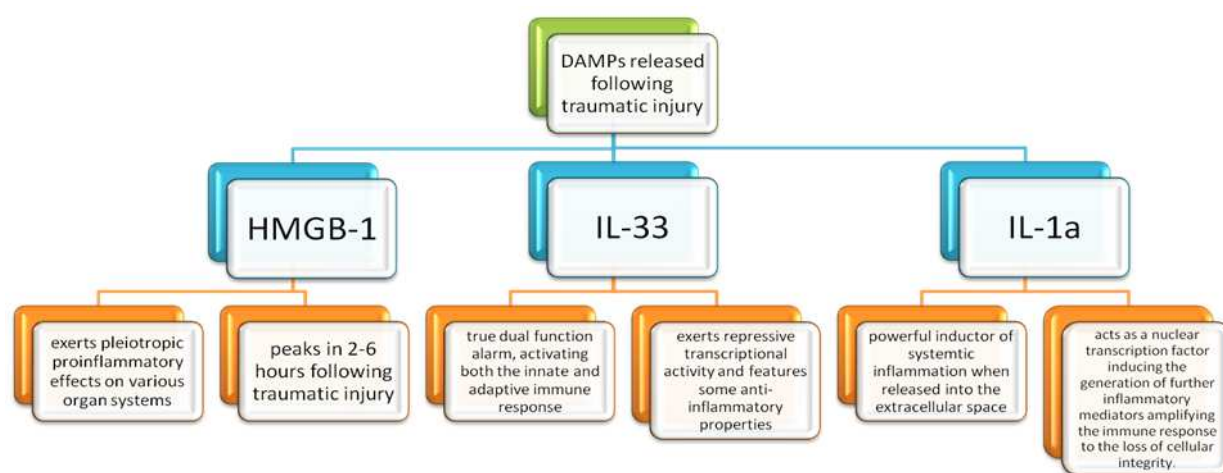

Fig. 2. Danger signals activating the immune response following traumatic injury

Role of Interleukin-1α (IL-1α)

Interleukins play a major role in the immune response; however their role is complex as they have both anti-inflammatory as well as proinflammatory properties. Following the breach of cellular integrity, IL-1a along with several other inflammatory cytokines illicit an amplified response characteristic of monocytes and macrophages enhancements of defensive functions in addition to co-stimulation of Natural Killer (NK) cells (Dinarello, 1991). As a dual function alarmin IL-1a activates an immune-modulatory response when released by cells of necrotic tissue, aside from its role in intracellular functioning in intact cells as a nuclear transcription factor. IL-1a is rarely intrinsically active and seldom secreted as an active moiety however its precursor molecule (pIL-1a) is biologically active (Dinarello, 1991). IL-1a is only secreted following the loss of cellular integrity and upon activation of monocytic cells, membrane calpain is activated and functions to cleave the precursor (pIL-1a) into the active constituent IL-1a (Wang *et al.*, 2004). Like 1L-33 but different in its activity from other members of the interleukin family, IL-1a serves as nuclear transcription factor aside from its role on intracellular and extracellular membrane receptors. As a transcription factor, IL-1a is able to induce downstream signaling to eventually produce NF-kβ and proinflammatory cytokines such as IL-6 and IL-8 (Werman *et al.*, 2004). A novel mechanism to block the immunomodulatory effects of IL-1a was performed in preclinical studies treating mice with clinically diagnosed SIRS and sepsis with IL-1 receptor antagonists and showed potentially promising results however it was unable to meet the primary endpoint of mortality reduction in a large double-blind, placebo controlled clinical trial (Dinarello, 2001). In summary, IL-1a is distinct from the other interleukins in regards to its role in traumatic injury, serving as a dual function alarmin. Not only does it produce a hyperinflammatory state, characteristic of many of the other interleukins upon release into the extracellular space but uniquely IL-1a serves as nuclear transcription factor which essentially amplifies the immune response through induction of the generation of further inflammatory mediators.

Role of Interleukin-33 (IL-33)

IL-33 represents the third dual function protein of the alarmin family and very similar in mechanism to HMGB-1 and IL-1a is released following cellular damage. Unlike IL-1a which is cleaved and activated to an active form, it has been elucidated that the fundamental actions of IL-33 is independent of caspase-1-cleavage and in fact, IL-33 may even be potentially inactivated by caspase-1 (Schmitz *et al.*, 2005; Cayrol and Girard, 2008; Talabot-Ayer *et al.*, 2009). As a cytokine and nuclear transcription factor IL-33 fulfills the definition criteria for a dual function alarmin. Unlike HMGB-1 and IL-1a which exert primarily inflammatory properties and increase transcriptional activity, IL-33 does the exact opposite through repressive transcriptional activity and like many of the interleukins, purports a degree of anti-inflammatory actions (Kunes *et al.*, 2010). Upon release into the plasma IL-33 is able to activate cells of the innate and adaptive immune response through interaction with specific receptors on the surface of T-Helper 2 (TH2) cells and mast cells, namely ST2 (Chackerian *et al.*, 2007). Upon interaction with ST2 receptor, IL-33 is able to illicit actions consistent with those of TH2, including amplified production of cytokines IL-5 and IL-13, both of which have anti-inflammatory properties. In addition IL-33 is functions as a chemotactic factor in the mobilization of TH2 to the site of action and equally as important, induces the differentiation of naïve T cells towards the lineage of TH2 phenotype production (Kurowska-Stolarska *et al.*, 2008; Komai-Koma *et al.*, 2007). IL-33 has implications in mediating anaphylactic shock as IL-33 is involved in the release of many inflammatory mediators, all of which are hallmark triggers of anaphylactic shock. IL-33 triggers the production and release of proinflammatory cytokines and chemokines such as IL-1β, IL-6, or TNF-alpha, promotes maturation and causes degranulation for further inflammatory mediation (De Vos and Frieri, 2015). To date there are no multi-centered trials that explicitly depict the beneficial or detrimental role of IL-33 in trauma however there is indirect evidence of its role in trauma where data has shown that patients who are clinically diagnosed with sepsis or experience a major trauma portray elevated levels of soluble receptors ST2, consistent with the activation of SIRS (Obeid *et al.*, 2007). To sum up the findings of IL-33 it is clear that this dual functioning alarmin activates both the innate and adaptive immune response leading to a multitude of immunologic responses. The actions of IL-33 are heavily dependent on the environment where it exerts either beneficial anti-inflammatory effects or exacerbates inflammatory process' present in traumatic injury.

Conclusion

The correlation between traumatic injury and sepsis is very complex and the exact immuneinflammatory mechanisms surrounding both processes are not fully understood. Loss of cellular integrity following injury activates the innate response characteristic of cytokine

storm and a state of hyperinflammation which has implications in remote organ damage and may lead to multi-organ failure. Sepsis, defined by the SIRS criteria, has many overlapping features of those seen in traumatic injury and is essentially indistinguishable from an immunological standpoint. Following severe trauma there is often an imbalance between inflammation and counter-regulation and increasing evidence suggest that damaged tissue plays a role in trauma induced immune dysfunction. The dual function alarmins HMGB-1, IL-1a and IL-33 represent fundamental mediators in both the initiation and continuation of the inflammatory response following the loss of cellular integrity as outlined in this review. The increasing role of mitochondrial which has its origin in bacteria, mimic bacterial infections by activating the immune response after cellular disruption, potentially changing the role of therapeutic interventions in traumatic shock focused on halting danger sensing and transmission of inflammatory mediators. Restorative strategies aimed at targeting DAMPs remain a novel area of research due to their role following tissue injury. The immunologic response to trauma shows great similarity to the systemic inflammatory response elicited in sepsis and treatment modalities should be targeted at treating the underlying cellular dysfunction in the immune response following the loss of cellular integrity. Future studies examining these novel therapeutic mechanisms surrounding traumatic shock are warranted and can offer potentially promising results to clinicians worldwide.

Author's Contributions

All authors equally contributed in this work.

Compliance with Ethical Requirements

William Heuser, Marianne Frieri, Krishan Kumar and Anthony Boutin declare that we have no conflict of interest.

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