Systemic inflammation and multiple organ injury in traumatic hemorrhagic shock

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1. ABSTRACT

Traumatic hemorrhagic shock (HS) is a severe outcome of traumatic injury that accounts for numerous traumatic deaths. In the process of traumatic HS, both hemorrhage and trauma can trigger a complex cascade of posttraumatic events that are related to inflammatory and immune responses, which may lead to multiple organ injury or even death. From a mechanistic perspective, systemic inflammation and organ injury are involved coagulation, the complement system, impaired microcirculation and inflammatory signaling pathways. In this review, we discuss the systemic inflammation and multiple organ injury in post-traumatic HS.

2. INTRODUCTION

Traumatic injury accounts for approximately 90,000 deaths per year in the US (1). Approximately 10% of traumatic deaths are preventable in rural civilians (2,3), 16% of which are due to hemorrhage (4). In this context, it is notable that traumatic injury is often accompanied by hemorrhagic shock (HS) (5), which can greatly worsen outcomes after traumatic brain injury (TBI) (6). Traumatic HS is independently associated with massive transfusion and increased mortality (7). In the clinical scenario, HS and TBI account for approximately 50% of all trauma-related deaths within the first 24 hours after hospital admission (8,9). In view of the burden of traumatic HS, a better understanding of the mechanism of tissue and organ injury after traumatic HS should enable the design of effective therapeutic strategies.

Both hemorrhage and trauma trigger a complex cascade of posttraumatic events related to inflammatory and immune responses (10). In the swine model of combined TBI and HS, the brain swelled around the lesion, showing local inflammation (11,12). In the murine model of HS induced by TBI, neuroinflammation occurred with increasing expression of cytokines and chemokines in brain tissue (13). Interestingly, the addition of HS to the inflammatory response in TBI resulted in a shift of the serum cytokine profile from pro-inflammatory to anti-inflammatory with significantly increased IL-10 levels, whereas the cytokine and chemokine profile in the brain was minimally affected (14). Evidence has emerged that the pattern of systemic inflammation may be different from the brain after HS. Therefore, we focus primarily, although not exclusively, on systemic inflammation and multiple organ injury after traumatic HS.

3. SYSTEMIC INFLAMMATION IN TRAUMATIC HEMORRHAGIC SHOCK

Trauma and especially multiple traumas can induce systemic inflammation, which is accompanied by increased plasma levels of inflammatory cytokines, such as interleukin (IL)-6, IL-8 and IL-10 (15). In a murine model of a combination of closed TBI, femoral fracture and hemorrhagic shock, systemic inflammation was increased, with a higher expression of tumor necrosis factor-alpha (TNF-alpha) and an increase in the number of CD8+ lymphocytes (16). The systemic post-traumatic inflammatory response was usually initiated in the animal HS model. Moreover, considering that several experimental protocols of systemic post-traumatic inflammatory model were reported in different studies, Pfeifer and colleagues (17) proposed that a murine model of pressure-controlled HS was more reliable for inducing a systemic inflammatory response than volume-controlled HS. The focus on the HS model suggests increasing attention on systemic post-traumatic
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4. MULTIPLE ORGAN INJURY IN TRAUMATIC HEMORRHAGIC SHOCK

Multiple organ injury is likely to be complicated with primary damage in acute trauma (18). Multiple organ dysfunction syndrome (MODS) is the leading cause of late death after traumatic injury, accounting for substantial morbidity and mortality (19,20). In view of MODS, which is partly due to excessive or maladaptive activation of inflammatory pathways (21), a better understanding of how inflammation participates in multiple organ injury post-trauma should enable the design of effective preventive strategies. In a multicenter prospective cohort study for investigating the outcome of 295 blunt injured patients with hemorrhagic shock, 50% of patients developed multiple organ failure (MOF). When the inflammatory response of these patients was modulated, the morbidity was increased (22). A multicenter prospective cohort study with severely injured and HS patients found that an increased IL-6 serum level in males was associated with an increased rate of MOF (23), suggesting a link between systemic inflammation and MOF after HS. Later, a prospective observational pilot study identified six candidate predictors of MOF, namely, inducible protein 10, macrophage inflammatory protein-1beta, IL-10, IL-6, IL-1Ra and eotaxin, all of which are inflammatory cytokines (24).

In the process of HS and MOF, several important organs may be injured. In addition to the brain, which has been discussed previously, organs such as the liver tend to be damaged by systemic ischemia. In HS, the rat model shows serum markers for liver damage, including aminotransferase and aspartate aminotransferase, were increased (25). Notably, in the rat model of non-alcoholic fatty liver disease, the pro-inflammatory state seems to prime the liver for hepatic ischemia after resuscitated HS (26). Moreover, the liver not only becomes damaged or dysfunctional from trauma-induced inflammation but also further perpetuates the inflammatory cycle (27,28).

5. IMMUNE RESPONSE IN TRAUMATIC HEMORRHAGE SHOCK

The inflammatory mediators are a part of the innate immune response in traumatic HS. As we mentioned before, the mouse model with hemorrhagic shock and multiple injury showed an increased population of CD8+ lymphocytes when their systemic inflammatory response was increased (16); the immune response was involved in the injury after trauma HS. Traumatic HS activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a cascade of defensive mechanisms, such as systemic inflammation and immunosuppression. In this process, after HPA activation, androstenetriol, a metabolite of dehydroepiandrosterone, provides a protective effect after a severe trauma HS, which is associated with an increased level of Th1 cytokines, while there is a decreased level of Th2 cytokines (29). This result suggests participation of Th1 and Th2 in the systemic inflammation and immune response. The inhibition of 5alpha-reductase results in the conversion of testosterone to 17beta-estradiol, which is beneficial for the post-traumatic immune response (30). Moreover, the lymphocyte sequestration agent FTY720 improves survival in experimental HS through elevating CD3+ lymphocytes in the mesenteric lymph nodes and spleen and disrupting lymphocytes, which...
reduce circulating and lung tissue infiltrating neutrophils and decreases the expression of liver immune-related gene expression (31) (Figure 1). Therefore, the strategy of lymphocytopenia in immunomodulation may ameliorate secondary immune injury in HS.

The innate immune response-related inflammation can promote cellular dysfunction and cell death in diverse tissues. As a marker of cellular injury and reduced immune function, the apoptosis in the spleen was investigated in an HS murine model, and the findings suggested that HS-induced apoptosis leads to post-traumatic immunosuppression through a biphasic caspase-dependent mechanism and implies a detrimental imbalance in the pro- and anti-apoptotic mitochondrial proteins Bax, Bcl-2 and Mcl-1 (32). Moreover, the 3% hypertonic saline solution has an immunomodulatory and metabolic effects for reducing the inflammatory response and attenuating end organ damage in the rat HS model (33), further demonstrating the immune response in the inflammatory response after HS.

6. MECHANISM OF SYSTEMIC INFLAMMATION AND MULTIPLE ORGAN INJURY

In the process from trauma to organ injury, HS or even death, our body experiences a series of microscopic to macroscopic changes. This process is like a black box in which the secrets of body changes are hidden. Several studies have tried to uncover the black box with various methods. Sillesen and colleagues (34) investigated the inflammatory and immunology mechanism after TBI and HS from the point of coagulopathy in a porcine model, and they found that the combination of TBI and HS can lead to coagulation and complement C5a to an immediate activation, causing endothelial shedding, protein C activation and inflammation. However, the pathway involved in the complement system requires further investigation. In contrast, the impaired microcirculation induced trauma injuries and an inflammatory response in patients with traumatic HS (35). The impaired microcirculation in the rat brain can be attenuated by aloe polysaccharides through inhibiting the systemic inflammatory response, leukocyte aggregation and lipid peroxidation (36), demonstrating the link between the systemic inflammatory response and impaired microcirculation. However, substantial future work is needed to clarify the link between microvascular alterations and organ dysfunction after traumatic HS.

Furthermore, Mollen and colleagues (37) searched for clues from inflammatory signaling pathways, studying toll-like receptor 4 (TLR4). TLR4 is from a highly conserved family of pattern recognition receptors, comprising 10 members in humans and 13 in mice (38), that plays a role in sterile inflammatory processes, including trauma, through recognizing a number of damage-associated molecular pattern molecules (39). Considering the role of TLR4 in sterile inflammation, Mollen and colleagues demonstrated the requirement for TLR4 signaling in post-trauma systemic inflammation and organ damage in both bone marrow-derived cells and parenchymal cells in chimeric mice (37). Though researchers have tried to clarify the mechanism of systemic inflammation in HS, the current understanding is not sufficient. Examination of individual signaling pathways may not be sufficient to explain the complex process of systemic inflammation that is involved in multiple organ injury. There may be an interaction between different signaling pathways in this process. It is still necessary to elucidate the mechanism of systemic inflammation and multiple organ injury in HS.

7. ANTI-INFLAMMATION IN TRAUMATIC HEMORRHAGE SHOCK

Though the mechanism of systemic inflammation and multiple organ injury in traumatic HS has not been clarified, advances in anti-inflammation could improve our understanding of systemic inflammation and multiple organ injury in traumatic HS. In patients visiting the emergency department for traumatic HS, polymorphonuclear leukocyte elastase can be reduced by treatment with ulinastatin (40). In the swine model of polytrauma and hemorrhagic shock, ascorbic acid can reduce the serum levels of TNF alpha and IL-6 (41). A study with a murine model showed that systemic inflammation and organ injury after HS are reduced by fresh blood products (42). In addition, a rat model had edema, congestion, inflammatory cell infiltration and necrosis in the heart, lung, liver and kidney tissue after treatment with exogenous hydrogen sulfide (43). All of these anti-inflammation agents may provide information in further research on the mechanism of systemic inflammation in traumatic HS.

The sodium-hydrogen exchanger (NHE) plays a role in intracellular pH recovery (44). Of the 11 known NHE isoforms represented in the human genome, NHE1 (also termed SLC9A1) is expressed in different organs (45). Several pre-clinical studies have found that specific inhibition of NHE1 could protect the heart from ischemia injury (46,47). In a similar condition of ischemia injury after traumatic HS, NHE-1 inhibition could facilitate the hemodynamic response to fluid resuscitation and attenuate tissue inflammatory injury and organ dysfunction, improving survival in the rat model (48). Wu and colleagues (49) further investigated the mechanism of NHE1 inhibition in the protective effect in traumatic HS, and they found that NHE1 inhibition could inhibit nuclear factor (NF)-kappaB activation and neutrophil infiltration as well as reduce iNOS expression and ERK1/2 phosphorylation, reducing systemic inflammation and multiple organ injury (Figure 2). In any case, irrespective of the methods that attenuate posttraumatic inflammation...
in HS patients, when systemic inflammation is controlled, MODS, leukocytosis and mortality are reduced, leading to a better prognosis for these patients (50).

8. CONCLUSIONS

In traumatic HS, systemic inflammation participates in multiple organ injury via inflammatory mediator secretion and cell infiltration. In this process, the innate immune response is stimulated in the form of the production and secretion of inflammatory mediators. Meanwhile, an acquired immune response is involved in systemic inflammation by the abnormal expression of Th1 and Th2 cells. Both immune responses in traumatic HS are the body’s response to the damage, which may protect our body from injury as well lead to secondary damage. Anti-inflammatory treatment can improve patients’ prognoses. However, the majority of results are based on animal models. Therefore, randomized and controlled trials with large sample of patients are needed in the future. Moreover, agents targeting systemic inflammation could be acting on a hub of signaling pathways. Despite the many challenges that remain, we are optimistic that a bright future lies ahead for improved understanding of and effective therapeutic strategies for traumatic HS.

9. ACKNOWLEDGEMENTS

This work was supported by Science and Technology Program from Hunan Science and Technology Burea (2012FJ4313).

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DOI: 10.1189/jlb.0407201


Key Words: Systemic Inflammation, Multiple Organ Injury, Hemorrhagic Shock, Review

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