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Review

The inflammatory basis of trauma/shock-associated multiple organ failure

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Abstract. Multiple alterations in inflammatory and immunologic function have been demonstrated in clinical and experimental situations after trauma and hemorrhage, in particular the activation of various humoral (e.g. complement, coagulation) and cellular systems (neutrophils, endothelial cells, macrophages). As a consequence of this activation process there is synthesis, expression and release of numerous mediators (toxic oxygen species, proteolytic enzymes, adherence molecules, cytokines), which may produce a generalized inflammation and tissue damage in the body. Mediators are responsible for ongoing interactions of different cell types and for amplification effects through their networks and feedback cycles, finally leading to a sustained inflammation and multiple organ damage in the body. In the setting of trauma/shock, many activators including bacterial as well as non-bacterial factors may be present that will induce local and systemic inflammatory responses. Although the potential role of bacteria/endotoxin translocation and its clinical relevance remains controversial, many lines of evidence support the concept that the gut may be the reservoir for systemic sepsis and subsequent MOF in a number of pathophysiologic states.

Key words: Complement – Neutrophil – Adhesion – Cytokines – Bacteria/endotoxin translocation

Introduction

Severe trauma, hemorrhage, and burns may initiate a cascade of events leading to septic complications, including multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF). MOF is the major cause of mortality in patients surviving initial resuscitation and surgical intervention following trauma/shock. Evidence is accumulating that MODS/MOF are the result of an excessive autodestructive inflammation, in which hypoxemia, tissue hypoxia/nonviable tissue, microorganisms/toxins and antigen/antibody complexes may be involved [1, 2]. In patients with polytrauma many bacterial and nonbacterial factors may be present that will induce local and systemic inflammatory responses.

Although inflammation is a well-described process in sepsis, the mechanism by which it becomes dysregulated to precipitate MOF is less well defined. In posttraumatic organ dysfunction different phases can be distinguished – the 'organ in shock' [3], early and late organ dysfunction, which are caused by generalized inflammation. Organ failure is the final result of the excessive action of inflammatory mediators, which result in a permeability increase as well as cellular dysfunction. Following a wide variety of stress responses, MOF is related to the effects of a multitude of mediators released from the humoral and cellular systems [4]. Essentially, the activation sequence consists of two phases: the primary events are immediately post-traumatic, and the secondary events start between three and seven days after insults, and in many cases are the consequences of sepsis. This 'two-hit' phenomenon [5] is thought to be due to a priming and activation sequence whereby the first stress enhances susceptibility to the second stress by priming inflammatory cells and cascades. In this setting, a second sub-injurious or mildly injurious stimulus promotes significant tissue injury, ultimately leading to vital organ dysfunction [6, 7].

Multiple alterations in inflammatory and immunologic function have been demonstrated in clinical and experimental situations after trauma and hemorrhage, in particular the activation of various humoral (e.g. complement, coagulation) and cellular systems (neutrophils, endothelial cells, macrophages) [4, 8]. As a consequence of this

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activation process there is synthesis, expression and release of numerous mediators (toxic oxygen species, proteolytic enzymes, adherence molecules, cytokines), which may produce a generalized inflammation and tissue damage in the body [9–11].

There is substantial evidence that both local and systemic inflammatory reactions may share a common mediator cascade pathway in the pathogenesis of diffuse tissue injury and organ dysfunction. In this review, we try to update our knowledge on inflammatory cell responses and the mediator network in trauma/shock-associated MOF.

Complement activation and its role in acute tissue injury

The complement system, which consists of a cascade of factors comprising about 4% of the total amount of plasma proteins, is divided into two pathways of activation, designated as the classical and alternative pathways. Both the classic and alternative complement enzyme systems participate in the host inflammatory response.

Complement activation occurs early in the setting of trauma/shock [12]. It leads to the release of biologically active substances, such as the anaphylatoxins C3a, C5a and the cytolytic terminal complement complex (TCC) C5-C9. The anaphylatoxins act particularly on granulocytes, resulting in activation of these cells. Furthermore, complement activation is involved in the inflammatory response via chemotaxis, opsonization, and phagocytosis [13].

During trauma or blood loss the complement system is activated via the alternative pathway. In both animal models and clinical situations complement activation can be readily demonstrated. In a dog model of hypovolemic traumatic shock, there was a significant decrease of total complement (CH50), suggesting that complement split-products are released at the same time [4]. Also, the degree of complement reduction is proportional to the severity of injury and the amount of tissue injured [14, 15]. In a group of moderately injured patients (injury severity score = 14), complement levels returned to normal in four to six days [16]. However, if complement activation is profound and persistent, such as after extensive injury or prolonged hemorrhage, a depletion of essential complement components is associated with deleterious effects, including an uncontrolled inflammatory state and progressive organ dysfunction [17]. On the other hand, in complement-depleted or complement-deficient experimental animals, the vital organ (lung) response to inflammatory stimuli is significantly diminished [18]. Therefore, patients with extensive tissue injury and massive complement activation are prone to have uncontrolled inflammation and subsequent ARDS/MOF. Thus the primary role of the complement system after trauma seems to be the coordination of the inflammatory response.

Activation of the complement system causes a variety of pathophysiologic alterations that contribute to the generalized systemic inflammation. The most important group of agents is formed by the anaphylatoxins C3a, C4a and C5a, which are potent mediators causing increased vascular permeability, smooth muscle contraction, aggravation of hypertension, stimulation of the release of histamine and arachidonate products, and adherence and aggregation of granulocytes to the vascular endothelium [3, 13, 19]. In addition, it has been demonstrated that C3a and C5a can induce tumor necrosis factor (TNF) and interleukin-1(IL-1) release in a dose-dependent manner, and enhance the release of these proinflammatory cytokines by endotoxin-stimulated macrophages/monocytes [20]. All these effects may involve the early activation of a complex cascade resulting in further cell damage and organ failure.

In patients with trauma the intensity of complement activation and the blood levels of elastase correlated with the following factors: injury severity, development of adult respiratory distress syndromes (ARDS), development and severity of MOF [8]. Similarly, C3a and TCC prediction of the development of MOF and the outcome can be made as early as the first day following trauma. Complement and polymorphonuclear neutrophil (PMN) activation (C3a, C3a/C3 ratio, and neutrophil elastase) were the most significant parameters, in a study of polytraumatized patients, to differentiate between survivors and non-survivors [21], similar to previous results [22].

Neutrophil activation and radical-related cell injury

The neutrophil is the most prevalent type of leukocyte present in the circulation, constituting the first line of defence against infectious agents or non-self substances that penetrate the body's physical barriers. Once an inflammatory response is initiated, neutrophils are the first cells to be recruited to the sites of injury or infection [23]. Although neutrophils are essential to host defence, they have also been implicated in the pathology of various acute insults and inflammatory states. Neutrophils may exert damaging effects through several mechanisms. After activation, neutrophilic polymorphonuclear leucocytes (PMN) generate and release numerous active substances, such as proteolytic enzymes (elastase, cathepsin G), reactive oxygen species (oxygen radicals, lipid-peroxidation products), and vasoactive substances (leukotrienes, eicosanoids, platelet-activating factor, PAF).

In a rat modified Wigger's hemorrhagic shock model, Barroso-Aranda and Schmid-Schönbein [24] reported that an increased number of activated circulating PMNs, as manifested by in-vitro nitroblue tetrazolium (NBT) reduction to formazan precipitates, was associated with the irreversibility of shock. Similarly, application of a 180 min shock model in the rabbit showed that mortality was associated with an increased level of spontaneous activation of circulating PMNs throughout the hemorrhagic period [25]. In a series of experimental studies, Moore and coworkers [26, 27] concluded that PMN priming and activation sequences appear to be important cellular processes to generate PMN-mediated tissue injury following intestinal ischemia reperfusion. Other evidence for neutrophil activation has been reported from clinical patients. For trauma patients, blood PMN chemiluminescence was higher than in controls throughout the posttraumatic course, while PMN recovered from the lung lavage fluid showed diminished activation [28]. Recently, the data from 17 high-risk patients indicated that major torso trauma primes and activates PMNs within 3 to 6 h after injury, suggesting that circulating post-injury PMNs, as mediators of hyperinflammation, may be

pivotal cells in orchestrating transitions from initial injury to subsequent systemic inflammation [10].

Compared with ex vivo measurements, analysis of plasma markers of PMN activation such as elastase permits detection of products released by circulating and adherent cells. In a baboon hypovolemic-traumatic shock model, there is a significant increase in plasma elastase levels both at the end of the shock period and after resuscitation [29]. Kushimoto et al. [30] further demonstrated that granulocyte elastase released during hemorrhage plays an important role in the pathogenesis of shock-induced mucosal lesions. There is a positive correlation between trauma severity and elastase plasma levels in patients [8]. Similarly, a significant correlation has been shown between sepsis and PMN-elastase plasma levels and the severity of MOF [8, 31], indicating that elastase appears to be involved in the local/systemic destruction of inflamed tissue causing severe tissue damage in patients with ARDS and/or MOF [32, 33]. These data suggest an important role for elastase as a marker of PMN activity, and possibly as a predictor of ARDS and MOF.

Although a number of inflammatory cascades have been incriminated in the pathogenesis of MOF, diffuse PMN-mediated tissue injury remains an attractive unifying concept [5, 10, 26]. The PMN is uniquely equipped to promote inflammation as well as cytotoxicity via oxygen-dependent and independent mechanisms [23]. Along with protease release, oxygen radicals produced by PMN can be used as an activation parameter. There are several important biological sources of oxygen radicals, but PMNs and xanthine oxidase (XO) appear to be the major sources in clinical disease states [34, 35]. Most recently, arginine deprived nitric oxide synthase was also found to be an important source of ischemia/reperfusion-induced superoxide production. Oxygen free radicals, such as superoxide anion, hydrogen peroxide, and hydroxyl ions are potent inflammatory agents inducing the process of lipid peroxidation, inactivation of enzymes (e.g. α-antiproteinase) and consumption of antioxidants (e.g. glutathione, tocopherol). Because of difficulties with the direct measurement of oxygen radicals, the indirect approach is much more frequently employed, including analysis of antioxidants, and lipid peroxidation products [36].

In the primate model of hemorrhagic-traumatic shock, tocopherol levels fell significantly during the shock period before retransfusion of shed blood, and remained below baseline until the end of study [36]. Shock-related studies of lipid peroxidation have been performed during extracorporeal circulation, in tissue of deceased polytrauma patients, and in polytrauma experiments [37, 38]. Reactive hydroxyalkenals such as 4-hydroxynonenal (HNE) are products of lipid peroxidation and increase in dog plasma after polytrauma and hypovolemia [39]. Moreover, circulating PMNs harvested from rats subjected to ischemia/reperfusion injury and then stimulated in vitro with chemoattractants release significantly more superoxide anion than PMNs harvested from sham-operated controls [40]. To further evaluate the potential role of oxygen radicals in the pathogenesis of trauma/shock-related organ failure, treatment strategies including antioxidants, scavengers, and iron chelators have been employed in animals studies. Cederna et al. [41] reported protective effects of allopurinol during 1 h hemorrhagic shock in rats. Similar findings were reported in dogs undergoing limited hemorrhage [42]. In a rat model of intestinal ischemia/reperfusion, the combination of superoxide dismutase (SOD) and catalase not only inhibited the generation of superoxide anions and hydrogen peroxide, but also limited the pulmonary and hepatic injury by 61% and 43%, respectively [43]. However, in a blinded placebo-controlled study, recombinant human SOD was used in a severe hypovolemic-traumatic shock model in baboon with no attenuation of the decrease in plasma tocopherol and sulfhydryl groups [44] and no block of organ damage, including intestinal injury. Although lipid peroxidation was attenuated by administration of enzyme conjugates in rats with zymosan-induced peritonitis, the mortality with SOD/catalase was actually increased [45]. In polytraumatized patients, a clinical trial of recombinant SOD failed to have a positive clinical impact [46]. In view of these findings, the relative importance of oxygen radicals for the pathophysiological sequence appears to be different in various types of trauma/shock. The true clinical relevance of superoxide radicals in producing cell and organ damage in the setting of acute insults, however, remains to be confirmed.

Endothelial-leukocyte interactions and adhesion molecules

The endothelium is known to be a very active participant in the process of inflammatory responses, including the regulation of blood flow, intravascular coagulation and adherence [47]. During the inflammatory process, the endothelial cells, in conjunction with leukocytes, appear to be involved in tissue injury. Increased neutrophil adhesiveness is a critical step in the sequence of events leading to neutrophil adherence to endothelial cells and neutrophil-mediated tissue injury [23, 34]. Endothelial-leukocyte interactions leading to microvascular-mediated organ damage may be a common pathway mediated by a diverse number of initiating factors, such as bacteria, endotoxin, cytokines, PAF/thrombin, TCC, and hydrogen peroxide as well as other oxygen radicals [48]. There is a growing body of evidence indicating that adhesion molecules expressed on the surface of both microvascular endothelium and neutrophils are the prerequisite for the initiation of the endothelial-leukocyte interactions associated with inflammatory states following trauma/shock [49, 50]. The endothelial adhesion molecules consist of the selectins (E-selectin, formerly known as endothelial leukocyte adhesion molecule-1 or ELAM-1; P-selectin, formerly known as granule membrane protein 140 or GMP-140) and molecules that belong to the immunoglobulin supergene family (e.g. intercellular adhesion molecule 1 or ICAM-1, vascular cell adhesion molecule-1 or VCAM-1) [51]. In addition, the bulk of available evidence implicates the leukocyte adhesion complex CD11/CD18 and L-selectin as the primary adhesion molecules of PMNs.

During the earliest phase of trauma/shock, adhesion molecules are responsible for the adherence of leukocytes to the endothelial cells, which may be crucial in endothelial cell injury leading to permeability changes and ultimately edema formation [48]. Increased expression of ICAM-1 on

endothelial cells has been associated with inflammatory disorders known to involve PMNs [52], and ICAM-1 up-regulation is sufficient to promote cytotoxicity via activated PMNs, representing a potential target for attenuating PMN-mediated injury to endothelial and other cells [53]. However, animals subjected to traumatic/hypovolemic shock showed only minimal expression of ELAM-1 after 6 h of shock, and this was much greater under septic conditions, perhaps due to the difference in circulating cytokine/endotoxin concentrations in the two models [54].

Regardless of the initiating factors during trauma/shock, endothelial-leukocyte interactions appear to be a common pathway leading to microvascular and tissue injury. For example, in patients with traumatic/septic shock, cytokines and/or endotoxin may potentiate organ dysfunction by inducing a change in endothelial cell phenotype from a non-inflammatory to a pro-inflammatory phenotype, leading to expression of adhesion molecules [54] and production of an enhancement factor, PAF [55, 56]. This shift in endothelial phenotype ultimately results in neutrophil sticking and transmigration due to endothelial-leukocyte interactions. Probably the most obvious sign of endothelial-leukocyte activation and interactions is leukostasis, demonstrated both in experimental and clinical posttraumatic situations [57]. Similar results were also found in baboon and rat models with hypovolemic shock, showing leukostasis in lung and liver tissues by measurement of myeloperoxidase activity [58, 59]. In this respect, more direct evidence has been obtained from splanchnic shock experiments in rats. Leukocyte adherence was noted upon reperfusion as judged by intravital fluorescence microscopy, and was attenuated by PAF antagonists in this model [60]. Furthermore, using this intravital microscopic approach, a significant increase in endothelial-leukocyte interactions in liver sinusoids after hemorrhagic shock was observed. Such an early inflammatory reaction in liver sinusoids may reflect an initiation process which probably contributes to subsequent organ failure [61].

Since neutrophil adherence to endothelium is cell-surface receptor-mediated, experimental studies have been carried out using antibodies directed against both neutrophil and endothelial cell-surface receptors. Blocking interactions between the CD11/CD18 complex and ICAM-1 with specific monoclonal antibodies has been shown to reduce tissue injury and organ dysfunction after hemorrhagic shock and ischemia/reperfusion in animal models [62, 63]. In addition to CD11/CD18 and ICAM-1, Garcia-Criado et al. [64] demonstrated that early modulation of the interaction between P-selectin and its ligand decreased neutrophil adhesion and migration and consequently diminished damage to the liver. In trauma patients it is difficult to directly examine the expression of endothelial-leukocyte cell adhesion molecules in various inflamed organs, but the detection of soluble, shed adhesion molecules in serum may also provide an indication of the extent of upregulation during the inflammatory response [65]. According to a report by Law et al. [49], a significant correlation was observed between the absolute levels of sICAM-1 at the time of resuscitation and the severity of subsequent MOF in severely injured trauma patients. Likewise, a subset of major trauma patients manifested elevated levels of circulating shed E-selectin and possibly P-selectin after injury and resuscitation, especially in those with lethal outcomes from infections and organ failure [66]. These data imply that endothelial-leukocyte cell interactions are upregulated immediately after injury and (based upon successful therapeutic intervention) may be implicated in the systemic inflammatory response that leads to MOF.

Potential role of cytokines in mediating systemic inflammatory response

MOF, resulting from a diffuse overwhelming inflammatory response, is ultimately mediated by the release of endogenous host factors. The role of cytokines, including TNF-α, IL-1, IL-6, in the pathophysiological condition of sepsis and MOF has been well established [67]. Such a concept is based on three major lines of evidence [68]: (1) Circulating levels of cytokines are present in animals and patients with sepsis, and these levels correlate with outcome; (2) Injection of inflammatory agents into humans and/or animals induces a septic response; (3) Experimental blockade of cytokines prevents organ injury and mortality that occur with sepsis. Unlike septic shock, however, the role of these cytokines in the pathophysiological alteration of trauma and hemorrhagic shock is not well delineated. Nevertheless, there is growing evidence suggesting that one of the important initiating events in post-traumatic/post-shock inflammation might be overproduction of proinflammatory cytokines, especially TNF-α, IL-1 and IL-6 [69–72].

The data regarding the participation of TNF-α and/or IL-1 in the response to trauma and hemorrhagic shock are less consistent, whereas IL-6 has been consistently shown to be elevated in patients with major surgery/trauma, or in animals secondary to blood loss or polytrauma, but its role beyond the induction of acute-phase proteins and procoagulation is not well defined. According to a report by Ayala et al. [73] using a mouse hemorrhage model, TNF was significantly increased during and up to 2 hours after blood loss. Similarly, studies by Rhee et al. [74] indicated an early appearance of TNF in rats with fixed-volume blood loss. As with endotoxin, a relationship was demonstrated between the TNF concentration in the systemic circulation and shock mortality after hemorrhage [75].These data are in accordance with other studies demonstrating that hemorrhagic shock significantly increased TNF plasma levels and enhanced the capacity of macrophages to release cytokines, including TNF, IL-1 in rats [70, 76, 77]. Likewise, it was found that Kupffer cells from animals subjected to trauma/hemorrhage produce more TNF and IL-6 in vitro [78]. Although circulating levels of IL-1 have not been detected after trauma/hemorrhage in most studies, remarkable amounts of IL-1β and TNF gene expression were observed in alveolar and peritoneal macrophages obtained both in the early or late phase of hemorrhage [71, 79]. In contrast to the positive detection of cytokines, Stylianos et al. [80] found that TNF was not detectable during 120 min hemorrhage in pigs or with combination of blunt trauma and hemorrhage, with or without fluid resuscitation. Although plasma TNF was detected only in a few cases in baboons following traumatic shock, including soft tissue trauma, fractures and hemorrhage for 3 hours [81], the levels of soluble TNF receptor (55 kDa) peaked between 1 and 2 h [82]. It may, therefore,

be possible that the lack of detectable plasma TNF levels is due to the binding of TNF to the cellular or soluble receptor. Plasma IL-6 levels, however, were found to be increased in this baboon model and peaked after 3–5 h [83].

There is less direct evidence for the role of pro-inflammatory cytokines in the development of the systemic inflammatory response syndrome among patients with trauma and/or hemorrhagic shock than there is for infectious patients. Nevertheless, several lines of evidence strongly implicate these mediators. Roumen and coworkers [69] reported that after injury trauma, hemorrhagic shock caused by a ruptured abdominal aortic aneurysm, or elective aortic aneurysm repair, increased concentrations of the cytokines TNF-α, IL-1β and IL-6 were a common finding. The higher values found in the early post-injury time course were associated with both increased mortality rates and an increased risk of subsequent ARDS and MOF. In another study, TNF-α, IL-6, and IL-8 levels increased significantly in patients during hemorrhagic shock when compared to healthy controls, although these levels were much lower than levels seen in patients during septic shock [84]. Recently, marked elevation of plasma TNF levels was found in multiple trauma/burned patients. Patients with MOF had high TNF levels compared with patients who failed to develop MOF [85]. However, many clinical studies have failed to show significantly increased circulating TNF levels in the setting of trauma and/or hemorrhagic shock, and these findings do not support a role for circulating TNF-α in the initial acute inflammatory response to trauma [83, 86, 87]. Only efficacy studies with anti-TNF treatment can provide final answers. The reasons for the discrepancy between the results of various studies are unclear, but may relate to the phasic nature of circulating TNF release, complex formation with soluble receptors, and possible predominance of local production of TNF. Cinat et al. [88] observed a sequential release of cytokine receptors and receptor antagonists after trauma, despite the absence of detectable levels of the primary cytokines themselves. In addition, some findings emphasize the concept that simply measuring circulating levels of the cytokines may not reflect local upregulation. For example, Suter et al. [89] measured concentrations of TNF and other inflammatory mediators in both the plasma and bronchoalveolar lavage fluid of patients with trauma or prolonged shock. They found that TNF levels in the bronchoalveolar fluid were markedly increased during all stages of ARDS, while plasma TNF levels remained within normal ranges. These data indicate that early local organ cytokine production may regulate the end-organ injury independent of the systemic cytokine response.

Much of the present knowledge about the important roles of TNF and IL-1 in sepsis has been derived from studies in which anti-cytokine antibodies were applied. Similarly, it seems that to demonstrate the contribution of cytokines in mediating systemic inflammation and organ dysfunction seen after trauma/hemorrhage, animal studies should be conducted with anti-cytokine measures, such as antibodies against TNF-α or IL-1 receptor antagonist. In this respect, passive immunization with a hyperimmune serum containing anti-TNF-α significantly neutralized TNF in both serum and peritoneal macrophages, and improved blood pressure response as well as survival rate in rats following acute hypovolemic hemorrhagic shock [70]. Further data showed that hemorrhage and resuscitation markedly increased the plasma TNF-α levels and that treatment with TNF-α monoclonal antibody, even 65 minutes after shock and after the initial formation of TNF had already occurred, significantly attenuated the cardiovascular consequences and organ injury and improved the survival of animals. [72]. Thus, it appears that in addition to the transient TNF release, detected at early points in time, a further sustained TNF formation may occur at a later stage of shock (even if not detectable, e.g. due complex formation) that plays an important role in the development of organ failure and outcome. Moreover, recent studies have shown that blockade of TNF-α prevents the lung injury after blood loss and attenuates multiple organ dysfunction associated with ischemic reperfusion injury to the bowel [90, 91]. Besides the beneficial effects of anti-TNF intervention, IL-1 receptor antagonist was able to block the detrimental response to hemorrhage and improved survival rate [92]. In addition, therapy with IL-1 receptor antagonist in the post-hemorrhage period was capable of normalizing the expression of some of the proinflammatory cytokines whose production among pulmonary cellular populations is increased by blood loss [93]. In the light of these findings, it can be concluded that overproduction of pro-inflammatory cytokines and activation of macrophage/monocytes, which escape regulatory control, may lead to a deleterious host response that culminates in the sustained inflammation and MOF related to severe hemorrhage.

Bacteria/endotoxin translocation and its relation to MOF

Today, the gut is not only regarded as an organ responsible for nutrient absorption, but also as an important metabolic and immunological system, functioning as an effective barrier against the residing luminal microflora and associated toxic by-products. In the past decade, there has been increasing recognition of the impact that severe injury and critical illness have upon the gastrointestinal tract and in turn, the influence that this complex organ can exert on metabolic and inflammatory responses. Although the potential role of bacteria/endotoxin translocation remains controversial, many lines of evidence support the notion that the gut may be the reservoir for systemic sepsis and subsequent MOF in a number of pathophysiological states [82, 94–96].

In general, impaired gut barrier function can be caused either during the shock period by decreased intestinal blood flow and reduced oxygen delivery, resulting during reperfusion in a stage of increased intestinal blood flow, or at a later stage again by reduced flow [97]. A variety of physiological stresses such as hemorrhagic shock, trauma, endotoxemia and thermal injury have been shown to cause failure of the gut mucosal barrier, with translocation of bacteria/endotoxin from the gastrointestinal into the mesenteric lymph nodes and, under conditions of sufficient ongoing stress, translocation into remote organs and systemic circulation [98–101]. This invasion of bacteria/endotoxin, into extraintestinal sites has led to the description of the gut as the motor of MOF, the so-called ‘gut

hypothesis' [102]. Support for the gut-origin hypothesis comes from several lines of investigation. Fine et al. [98] initially proposed that in hemorrhagic shock the gut becomes the source of endotoxin and invasive gram-negative bacteria and in the presence of a defective reticuloendothelial system leads to systemic infection. In a series of studies, Deitch and coworkers [103] later demonstrated that enteric bacteria can escape from the gut and induce both non-lethal and lethal systemic infection. It has been shown in a rat model of hemorrhagic shock that the duration of hypotension is related to mucosal injury, the magnitude of bacterial translocation and the mortality rate [104]. This phenomenon has been noted after hemorrhage/trauma in different species, including rats, rabbits, dogs and baboons [75, 77, 99–101, 105, 106]. In a series of experiments, bacterial translocation into the small intestinal wall was found in rats subjected to hemorrhage as early as at the end of resuscitation [75]. Similarly, the highest bacterial counts were noted in mesenteric lymph nodes, followed by the liver and spleen, in baboons after hemorrhagic/traumatic shock [99]. Positive blood cultures were noted in both the acute and chronic experiments during the hemorrhage and/or reperfusion period [99]. These results obtained in a subhuman primate model are in agreement with reports of bacterial translocation, mainly in rodents and provide further evidence that the phenomenon of translocation may not be limited to rodents.

Endotoxemia is relatively common following mechanical trauma, shock and burns and is associated with various conditions leading to MOF [95, 107, 108]. In addition, endotoxin has been shown to impair host defences, increase gut mucosal permeability and enhance the process of bacterial translocation [109, 110]. Thus, endotoxemia, in its turn, aggravates the disturbance of gut barrier function, thereby generating a recurrent circle of gut-derived infection. Studies in rats subjected to hemorrhagic shock indicated that endotoxemia was present in 33% of animals after only 30 minutes of shock, and in 88% of animals after 2 h of shock [107]. Experiments also documented the significance of the early appearance of endotoxin in the systemic blood following hemorrhage and/or trauma in both rodents and primates [75, 77, 82, 83, 101, 111]. The rat studies revealed a marked, albeit transient, increase in plasma endotoxin concentrations, both in the portal and systemic circulation following hemorrhagic shock, suggesting that the endotoxin translocated from the gut at the early stage might be transported, at least in part, to the liver via the portal route [75]. In rabbits, abnormally high endotoxin levels were noted in the systemic blood samples as a result of hypotensive insult, but the changes were much more pronounced in animals with MOF when compared with those without MOF at the end of shock and thereafter [112]. Likewise, elevated plasma endotoxin levels were found in hemorrhagic/traumatic shock baboons at the end of a 3-h shock period and 1 h after reinfusion [111]. This finding was further confirmed in a subchronic model in baboons consisting of oxygen debt-controlled hemorrhage together with an infusion of zymosan-activated plasma [82, 111].

If invading enteric bacteria and endotoxin are indeed the reason for the development of the systemic inflammation response syndrome, then therapy directed at preservation of barrier function and/or elimination of potential bacteria/endotoxin translocation would be expected to decrease the incidence of organ dysfunction and subsequent mortality. There are several measures that control or eliminate translocated bacteria/endotoxin [113], which have been used in experimental studies to evaluate the potential role of translocation events in the pathogenesis of sepsis and MOF associated with acute insults. In a prolonged hemorrhagic shock model (mean arterial pressure at 30–35 mmHg for 3 h) in rats, animals were treated with recombinant bactericidal/permeability increasing protein ($rBPI_{21}$), a well-described bactericidal and endotoxin-neutralizing protein [101]. Treatment with $rBPI_{21}$ neutralized systemic endotoxemia, attenuated the damage in vital organs, and reduced 48 h mortality in rats after severe hemorrhage [101]. With the same model, administration of an anti-core endotoxin monoclonal antibody (WN1 222-5) also provided noticeable protection of organ damage and significantly improved the survival rate from 21% to 71% [82,114]. This observation is in accordance with reports in which Re-lipopolysaccharide antiserum, polymyxin B and selective decontamination of the digestive tract, were found to reduce the incidence of translocation and improve the survival rate in animals suffering from severe injury [77, 106, 115]. Recently, Boermeester et al. [116] reported that in partially hepatectomized rats, a systemic inflammatory response and its clinical hemodynamic/biochemical sequelae triggered by endogenous endotoxemia were blunted by the administration of $rBPI_{23}$. Taken together, these results suggest that bacteria/endotoxin translocation may play an important role in the development of multiple organ dysfunction resulting from trauma/hemorrhage. Gut-derived endotoxin/bacteria has been incriminated as a prime factor for the release of cellular mediators that may in turn, activate or further perpetuate systemic inflammatory response to injury.

In a rat hemorrhage model, significant increases in plasma TNF level and IL-1 activity of peritoneal macrophages were shown in the controls after resuscitation, but markedly prevented by the administration of polymyxin B before induction of shock [77]. In another experiment, we found that the significant rise in TNF levels in the portal vein occurred prior to the elevated levels in the systemic blood after hemorrhage, indicating gut-derived cytokine formation, for which the gut-associated macrophages in the lamina propria of the intestine can be considered a potential source [117]. New evidence shows that the gut generates inflammatory cytokines, including TNF and IL-6 in response to shock and an inflammatory stimulus [117, 118], and that proinflammatory gene expression occurs in Peyer's patches both during and after hemorrhage/resuscitation [119, 120]. More recently, an experimental study has shown that an increase in whole blood monocyte TNF response after hemorrhagic shock is mediated via the endotoxin/ CD14 pathway [121]. Collectively, it has been postulated that gut-associated macrophages constitute the major source for cytokine formation at the early stage of shock, and that the Kupffer cells stimulated by bacteria/endotoxin transported to the liver via portal blood serve as the important cellular source for the circulating cytokine at a later stage [95]. In contrast to these data, failure to detect enteric bacteria/endotoxin translocation has been reported by other authors. Studies by Ayala et al. [73] and Rhee et al. [74] had shown that hemorrhage in mice and rats seemed to induce an early cytokine release, but without any detectable amount of

endotoxin in blood. The lack of detectable endotoxin in those experiments could probably have been the result of several factors: (1) systemic samples rather than portal samples were used for assay; (2) endotoxin level below the detection limit of the method; and (3) rapid clearance from the systemic circulation by the reticuloendothelial system. Nonetheless, in the setting of shock, hypoxia may also contribute to the induction of cytokines.

Extensive work on bacteria/endotoxin translocation has been performed in animals and occurs notably in the above experimental models. It is difficult, however, to extrapolate these results to humans. As a result, their clinical significance remains controversial. Rush et al. [107] reported a significant correlation between positive blood cultures and the degree of hemorrhagic shock in patients. In a study by Cabie et al. [122] which measured endotoxin and cytokines in systemic and portal blood of patients undergoing abdominal aortic surgery, portal endotoxin was detected even after bowel manipulation but was elevated especially during the reperfusion phase. Similarly, substantial plasma endotoxin levels were found in patients with major trauma and severe hemorrhage, and endotoxemia was often related to ARDS and acute renal failure [123]. Most recently, a clinical study showed that the mean plasma endotoxin concentrations of nine non-survivors were significantly higher than those of 16 survivors on day 1 and 7 postinjury [85]. In addition to the above mentioned studies, there are some clinical reports that intestinal permeability, as a measure of gut mucosal barrier function, may be increased following trauma, hemorrhage and thermal injury [124,125]. Despite this evidence, attempts to apply the gut-origin hypothesis in the clinical setting have yielded conflicting results. Moore et al. [126] inserted portal vein catheters for sequential blood sampling in 20 injured patients requiring emergency laparotomy and who were at known risk of MOF. This prospective clinical trial could not confirm portal or systemic bacteremia and/or endotoxemia within the first 5 days after injury, despite an eventual 30% incidence of MOF. Peitzman et al. [127] also demonstrated that bacterial translocation to the mesenteric lymph nodes was not a common occurrence in acutely injured trauma patients. Similarly, elevated plasma endotoxin levels were not detected in patients with hemorrhagic shock and severe blunt trauma [69,84]. Changes in intestinal permeability were not consistently correlated with the development of septic complications [124]. On the other hand, no convincing reduction in morbidity or mortality has been shown in most clinical trials despite a consistent decrease in the infection rate as a consequence of the selective decontamination of the digestive tract [36]. Therefore, it seems that the clinical significance of bacteria/endotoxin translocation remains an open question. It is still unknown whether systemic inflammatory response and subsequent MOF can be prevented, at least in part, in critically ill patients by maintaining the gut mucosal barrier and limiting the translocation process. Thus, only clinical studies with new therapeutic regimens (e.g. $rBPI_{21}$) may provide further information for the clinical relevance of BT and the role of the intestine in the development of MOF. Positive results have been obtained in a phase II trial (presented by XOMA at the Sixth Vienna Shock Forum) which is currently being followed by a phase III trial.

Conclusion

MOF is the leading cause of mortality in patients surviving initial resuscitation and surgical intervention after trauma/hemorrhage. The post-traumatic sepsis and MOF are recognized to be a result of overwhelming inflammation. Multiple alterations in inflammatory and immunological function have been demonstrated in clinical and experimental situations following polytrauma and/or hemorrhagic shock. In particular, there is activation of various humoral systems (e.g. complement, coagulation) and cellular systems (e.g. neutrophils, endothelial cells, macrophages/monocytes) in the course postinjury. As a consequence of this activation process, synthesis, expression, and release of numerous inflammatory mediators (e.g. toxic oxygen species, proteolytic enzymes, adherence molecules, cytokine, etc.) occurs. These mediators are responsible for ongoing interactions between different cell types and for amplification effects through networks and feedback cycles, finally leading to a sustained inflammation and multiple organ damage throughout the body. In the setting of trauma/shock, many activators, including bacterial as well as non-bacterial factors, may be present that will induce the local and systemic inflammatory responses. Although the potential role of bacteria/endotoxin translocation and its clinical relevance remains controversial, many lines of evidence support the concept that the gut may be the reservoir for systemic sepsis and subsequent MOF in a number of pathophysiological states. In fact, MOF as a result of severe injuries or blood loss is a complex syndrome which simplistic mechanistic theories cannot adequately define. Dysregulation of the host's inflammatory response mechanism(s) plays a critical role in the initiation and perpetuation of this perplexing organ failure complication. Continuing advancement and understanding of the molecular biological events that regulate the inflammatory response will allow us to clarify the relationship between initial injury, deleterious cascades, and subsequent MOF.

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