Cell Stress and Chaperones (2018) 23:483–489
https://doi.org/10.1007/s12192-017-0859-9

MINI REVIEW

An overview of cytokines and heat shock response in polytraumatized patients

Maria Concepción Guisasola[1] · **Berta Alonso**[2] · **Beatriz Bravo**[3] · **Javier Vaquero**[2,4] · **Francisco Chana**[2,4]

Received: 25 August 2017 / Revised: 20 October 2017 / Accepted: 20 October 2017 / Published online: 3 November 2017

Abstract Early after injury, local tissue damage induces a local and systemic inflammatory response that activates the immune system and leads to the development of systemic inflammatory response syndrome (SIRS). This post-traumatic response often results in uncontrolled release of inflammatory mediators and over-activation of the immune system, which occasionally results in multiple organ dysfunction syndrome (MODS). In parallel, a state of immunosuppression develops. This counter-regulating suppression of different cellular and humoral immune functions has been termed "compensatory anti-inflammatory response syndrome (CARS)." Both SIRS and CARS occur simultaneously even in the initial phase after injury. Pro- and anti-inflammatory cytokines have been suggested to play a major role in development of SIRS, although the degree of involvement of the different cytokines is quite disparate. While TNF-α and IL-1β are quite irrelevant for predicting organ dysfunction, IL-6 is the parameter that best predicts mortality. The hyperinflammatory state seems to be the cause of post-traumatic immunosuppression and heat shock proteins (HSPs), which have been proposed as one of the endogenous stimuli for the deterioration of the immune system acting as danger-associated molecular patterns (DAMPs). Extracellular HSPA1A released from injured tissues increase up to ten times immediately after trauma and even more in patients with MODS. It has powerful immune properties that could contribute to post-traumatic immunosuppression through several mechanisms that have been previously described, so HSPs could represent trauma-associated immunomodulatory mediators. For this reason, HSPA1A has been suggested to be a helpful early prognostic biomarker of trauma after severe injury: serial quantification of serum HSPA1A and anti-Hsp70 concentrations in the first hours after trauma is proposed to be used as a predictive biomarker of MODS and immunosuppression development in polytraumatized patients.

✉ Maria Concepción Guisasola
mguisasola@hggm.es

Berta Alonso
bertalpol@gmail.com

Beatriz Bravo
beatriz.bravomolina@ceu.es

Javier Vaquero
vaquerocot@gmail.com

Francisco Chana
selvanegraphd@yahoo.es

[1] Servicio de Medicina y Cirugía Experimental, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Hospital General Universitario "Gregorio Marañón", Dr. Esquerdo 46, 28007 Madrid, Spain

[2] Servicio de Cirugía Ortopédica y Traumatología, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Hospital General Universitario "Gregorio Marañón", Dr. Esquerdo 46, 28007 Madrid, Spain

[3] Instituto de Medicina Molecular Aplicada. Facultad de Medicina, Universidad San Pablo-CEU, Ctra de Boadilla del Monte km. 5,300 Boadilla del Monte, 28668 Madrid, Spain

[4] Departamento de Cirugía. Facultad de Medicina, Universidad Complutense, Plaza de Ramón y Cajal, 28040 Madrid, Spain

Keywords Polytrauma · Inflammatory response · Post-traumatic immunosuppression · Cytokines · Heat shock proteins · DAMPs

Introduction

Despite the therapeutic advances in prehospital care and intensive care units, polytrauma continues to be the leading cause of death in subjects under 45 years of age (Demetriades et al. 2004). This results in an enormous financial burden due to the long stays in intensive care units, the need to undergo various operations, and the healthcare and social management of the sequelae of polytrauma patients, which in 1994 amounted to 20 billion pounds in the UK (Sikand et al. 2005).

Early mortality following polytrauma is primarily caused by massive blood loss and severe brain injury. Late mortality is caused by secondary brain injury and by host defense or multiple organ failure (von Rüden et al. 2013). In the initial phases after injury, local tissue damage caused by contusions, lacerations, hypoxia, or hypotension induces a local and systemic inflammatory response intended to preserve immune integrity and to stimulate repair mechanisms. The damage to the cells induces the release of so-called danger-associated molecular patterns (DAMPs) (Keel and Trentz 2005). These DAMPs lead to immune system activation and to the development of the systemic inflammatory response syndrome (SIRS) (Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. In: American College of Chest Physicians/Society of Critical care Medicine Consensus Conference 1992). Furthermore, the reperfusion leads to an increase in reactive oxygen species that also induce an immune response. Depending on severity of the aggression and on the immune status of patients, the post-traumatic response often leads to the uncontrolled release of inflammatory mediators that injure tissues, and to over-activation of the immune system, sometimes causing multiple organ failure (multiple organ dysfunction syndrome, MODS) (Lausevic et al. 2008; Namas et al. 2015); MODS is a dreaded complication in post-traumatic polytrauma patients (Cherry et al. 2007).

In addition, soon after trauma, a state of immunosuppression develops to a degree correlating with the severity of the trauma. This counter-regulating suppression of different cellular and humoral immune functions has been termed "compensatory anti-inflammatory response syndrome (CARS)." Both SIRS and CARS occur in parallel even early after injury. The immunosuppression is responsible for the increased risk of infectious complications in severely injured patients.

The role of cytokines

Research over the past decade has suggested a major role of pro- and anti-inflammatory cytokines in SIRS development (Sousa et al. 2015). Cytokines are signaling molecules of the immune system, which are secreted by the different cells of the immune system. Other cells, such as endothelial cells, are also able to produce cytokines to interact with the immune system. In acute immune response, the cytokine tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β are primarily secreted. These induce the secondary immune response, where IL-6 and the anti-inflammatory IL-10 are released (van Griensven 2014). Patients with systemic inflammation have shown elevated serum levels of TNF-α, IL-1β, or IL-8, whereas IL-6 has been correlated to the injury severity score (ISS), incidence of multiple organ failure, sepsis, and survival prognosis (Cuschieri et al. 2010).

In the first hours, proinflammatory cytokines activate recruitment and phagocytic activity of polymorphonuclear leukocytes (PMNLs), the first line of immune defense, and stimulate PMNLs to release free oxygen radicals. An increase occurs in the production of granulocytes and their release to peripheral blood from the bone marrow, as well as a reduction in PMNL apoptosis that results in leukocytosis during SIRS, irrespective of the presence of sepsis (Tidball 2005). It has been shown that 92% of patients with severe injuries develop a SIRS response during the 1st week of hospitalization and that this leukocytosis is not correlated with the possible presence of bacteremia (Claridge et al. 2010). In a former study by our group, 18 patients who met the defining criteria for polytrauma with a score in the abbreviated injury scale greater than 2 in at least two body regions of the ISS (Kelly et al. 2014) and an ISS greater than 16 (Keel and Trentz 2005) were included. Data collection was performed at hospital admission and 12, 24, and 48 h post-trauma. All patients, with or without MODS, had significant leukocytosis in the first 24 h after admission (Butcher et al. 2013) as part of the SIRS response.

Proinflammatory cytokines also activate the coagulation cascade along both the classical pathway and the intrinsic coagulation system. In the initial phase, enhanced thrombin formation increases fibrinogen cleavage and reduces fibrin monomers from polymerizing to form stable fibrin clots (hypercoagulability), which is why fibrinogen depletion is observed (Guisasola et al. 2015). In the following hours, in the presence of tissue hypoperfusion and significant thrombin generation, the endothelium expresses thrombomodulin, which triggers a "thrombin switch" by which thrombin is no longer used for fibrin generation, but to produce activated C protein and early systemic anticoagulation. Since less thrombin is available to cleave fibrinogen, higher fibrinogen levels are detected in plasma (Wirtz et al. 2017), in line with our own findings. However, pathological findings suggesting disseminated intravascular coagulation are exceptionally uncommon

in trauma and were not seen in any of the study patients (Rizoli et al. 2011).

The main effect of IL-6 is to induce synthesis of acute phase proteins in the liver, such as C-reactive protein (CRP). Increased CRP levels are apparent 8 h after the trauma and peak values are usually reached at 48 h (Mimoz et al. 1998). The decrease in CRP is parallel to the resolution of the stimulus giving rise to it, whereas persistence of an elevated CRP level indicates that the inflammatory process persists. In our study, CRP concentration was higher than normal on admission to the emergency department and gradually increased until reaching peak values at 48 h. However, various studies have found no correlation between serum CRP concentration and trauma severity or prediction of survival in polytraumatized patients (Mimoz et al. 1998). The presence or not of MODS did not cause significant changes in plasma levels of leukocytes or fibrinogen or in serum CRP of our patients, so their significant increase after polytrauma may be only explicable in the context of SIRS, irrespective of other possible associated complications.

The degree of involvement of the different cytokines in the clinical course of polytraumatized patients is quite disparate. In this, there is a bias factor resulting from the half-life of each cytokine, the time of its peak production, and the time when blood samples are taken in each study. TNF-α and IL-1β are considered hyperacute proinflammatory cytokines with effects 1–2 h after the polytrauma, whereas both IL-8 and IL-6 are subacute cytokines, with peaks between 1 and 4 h after the aggression and subsequently sustained levels that make them more easily detectable than TNF-α and IL-1β (Giannoudis et al. 2004).

TNF-α has a short half-life in plasma of 14–18 min, peaks in 1 or 2 h being fundamental in the activation of SIRS, and may have significantly decreased at 4–6 h, which might reduce its role in the severity assessment with contradictory results reported in literature (Giannoudis et al. 2004; Ciriello et al. 2013) and makes pre-analytical management very important. Most TNF-α studies available in patients with multiple injuries have focused on the clinical course of patients with septic shock secondary to abdominal pathology admitted to intensive care units, in which the results of use of TNF-α as predictor of sepsis and mortality have been disappointing, but this sequential pattern of release has not been found in trauma (Dekker et al. 2016). It can be concluded that TNF-α has little value for predicting injury severity or outcome or to predict development of MODS (Weckbach et al. 2012).

IL-1β acts by inducing fever, hypotension, endothelial cell adhesion as a procoagulant, and chemotaxis of PMNs and macrophages, and works synergistically with TNF-α. The half-life of IL-1β is approximately 10 min, which makes its detection after trauma more unlikely. Therefore, the pre-analytical problems for IL-1β are similar to those for TNF-α. In our study, it was undetectable in the control group but could be detected in polytraumatized subjects, without variations in the times studied and without discriminating between patients with or without MODS. This is in line with the results reported by other researchers who, after studying the cytokine profile in 143 patients with an ISS ≥ 16, concluded that IL-1β has no value for predicting organ dysfunction (Frink et al. 2009).

IL-6 is a secondary cytokine that is induced by TNF-α, IL-1β, and other factors. It is less transient and therefore more easily measured than either TNF-α or IL-1β. High levels of IL-6 have been shown as of the 1st hour after trauma and remain for a few days (Giannoudis et al. 2004). IL-6 is currently considered as the most accurate prognostic marker of outcome in trauma patients with SIRS, sepsis, or MODS (Volpin et al. 2014; Pape et al. 2007). In fact, Frink et al., after a logistic regression analysis, demonstrated that IL-6 not only was correlated with the risk of MODS but also predicted MODS development with an overall accuracy of 84.7%, and that IL-6 was the parameter that best predicted mortality, with an accuracy of 86.1% at day 1 and 83.2% at day 2 (Frink et al. 2009).

IL-6 also has anti-inflammatory properties, both due to the induction of the release of prostaglandin E2, a powerful endogenous immunosuppressant, by macrophages (Tilg et al. 1997), and to the promotion of the release of IL-1β and TNF-α receptor antagonists (Frolov et al. 2013). This, together with the production of specific anti-inflammatory cytokines such as IL-10 and IL-4, causes the initial proinflammatory cell-mediated immune response of the innate immune system to be followed by a CARS, which is mediated by cells from the acquired immune system. This hyperinflammatory state appears to be the cause of post-traumatic immunosuppression and increased susceptibility to infections and septic complications (Reikeras 2010); it has also been called *sterile inflammation*, due to the absence of bacterial infection at the time of the traumatic event. Immune system deterioration has led to the suggestion that this post-traumatic immunosuppression should be triggered by endogenous stimuli, among which heat shock proteins (HSPs) have been proposed (Flohé et al. 2007a, b).

The heat shock proteins

Heat shock or stress response is the name given to a highly preserved cell response to injury. It is a cell defense mechanism characterized by an increased expression of heat shock or stress proteins that increase cell protection from aggressions that would otherwise prove fatal. HSPs, constitutively expressed by all cells, are essential for significant cell processes such as protein folding, protein protection from denaturation or aggregation, and facilitation of protein transport through membrane channels (De Maio 1999; DeMeester

et al. 2001). Although HSPs were considered for some time as intracellular molecules that could only be released to the extracellular medium from necrotic cells by a passive mechanism (Calderwood et al. 2007), it is currently known that they may be released by non-necrotic cells via an active mechanism including the non-classic protein release pathway, through which HSPs are released both as free proteins and within highly immunogenic exosomes (Asea 2008). Within the HSP superfamily, the most widely studied family of proteins related to the biology of inflammation is HSPA1A (Hsp70) (Kampinga et al. 2009). HSPA1A has been shown to be present in the serum of normal subjects (Dulin et al. 2010), and circulating HSP levels have been found to be increased in patients with some types of cancer, cardiovascular disease, renal disease, and acute conditions such as infections, and in severely injured patients (Zhang et al. 2011; Chebotareva et al. 2017; Koliński et al. 2016; Pittet et al. 2006).

Extracellular HSPA1A has powerful immune properties: it activates the classical complement pathway, participates in exogenous antigen processing and presentation, and shows immune reactivity to endogenous HSPs (Pockley et al. 2008). It can also have an immunostimulatory effect and activate the host inflammatory response. As such, HSPs are involved in the acquired immune response by enhancing antigen processing and presentation through the MHC class II pathway, and also in the innate immune response, as they have been found to be involved in bacterial lipopolysaccharide recognition. As early as 2–4 h after exposure of antigen-presenting cells (APCs) to exogenous HSPA1A, significant amounts of cytokines such as TNF-α, IL-1β, IL-6, and IL-12, and GM-CSF, nitric oxide, and chemokines, including MIP1, MCP1, and RANTES, are released. To sum up, multiple data are available suggesting that HSPs are potent inducers of inflammatory events (Asea 2008).

As stated above, extracellular HSPs released from destroyed tissue and damaged cells can activate the host inflammatory response: this effect is the so-called first-hit phenomenon of the two-hit theory and occurs very early after trauma (Giannoudis 2003). In 29 patients who met at least two of four conventional criteria for SIRS, extracellular HSPA1A levels were significantly higher than in a control healthy-volunteers group and correlated with the severity of illness (Vardas et al. 2014), which leads the authors to suggest that these findings reinforce the hypothesis that extracellular HSPs may act as danger signal to modulate the immune system. In a previous study of our group (Guisasola et al. 2015), HSPA1A serum concentrations up to ten times higher immediately after injury were observed in polytraumatized patients (ISS > 16) versus control subjects, levels that remain elevated until 48 h after the accident following a time-kinetics concordant with that previously described (Pittet et al. 2006). The reported biological half-life of HSPA1A is 18 h (Gerner et al. 2002; Brøchner and Toft 2009), which suggests that persistence of its levels may be due to continuous release and/or delayed clearance from circulation of the protein. The high extracellular concentration of HSPA1A was even greater in patients with MODS. Although our research did not include follow-up of survival after hospital discharge and all patients except one survived during admission, the greater elevation of extracellular HSPA1A in patients with MODS corroborates the proinflammatory role of this protein in situations of severe trauma reported by other authors, who also correlated it with survival and morbidity (Vardas et al. 2014; Dehbi et al. 2010).

Therefore, it can be suspected that the release of HSPA1A into serum could provide the body with a way to monitor the extent of damage to organs and tissues after trauma and that, as its plasma levels have been found to be associated to MODS and death, HSPA1A could possibly be a useful prognostic trauma biomarker early after severe injury of the degree of injury suffered by trauma patients (Ren et al. 2016). Patients with HSPA1A who have concentrations up to ten times higher than the normal would be candidates for submission to a "damage control surgery" as a treatment strategy of temporization which radically increases the survival in these most seriously injured patients (Lamb et al. 2014).

In parallel to the hyperinflammation cascade, a state of immunosuppression rapidly occurs after trauma; it is termed "compensatory anti-inflammatory response syndrome (CARS)" and it is associated with increase production of anti-inflammatory cytokines and the development of immunosuppression (Binkowska et al. 2015), that in turn is responsible for the increased risk of infectious complications in severely injured patients (Probst et al. 2009; Reikeras 2010; Xiao et al. 2011). Nevertheless, and despite the research carried out in recent years, the exact mechanisms involved in suppression of several cellular and humoral immune functions remain unclear. Matzinger formulated its "danger theory" in 1994 (Matzinger 1994) and according to it, danger signals are part of a model of immunity; the immune system responds to substances that cause damage and these alarm signals are molecules released by cells undergoing stressed or injured tissues; these molecules are sensed by resting antigen-presenting cells (APCs) and induce APCs to become activated and to initiate immune response (Matzinger 1998; Gallucci and Matzinger 2001). Since then, several authors have proposed HSPs as good candidates to be alarmins: HSPs can activate dendritic cells and macrophages in the absence of foreign pathogens to trigger an innate immune response and can act as chaperones to participate in the adaptive immune response making the HSPs the first large family of endogenous danger signals and a prime example of DAMPs (Osterloh and Breloer 2008; Borges et al. 2012, 2016).

The group of Flohe (Flohé et al. 2007a, b, 2008) proposes that HSPs released from injured tissues could contribute to the immunosuppression that is observed after multiple injuries,

and this activity may be explained through several mechanisms. On one hand, Toll-like receptors (TLRs) are the primary sensors of pathogen invasion, and signal initiation of both innate immune response and development of antigen-specific adaptive immunity. After injury, increased expression of TLRs located on macrophages and neutrophils have been described (Binkowska et al. 2015). Trauma releases HSPS that bind to TLR2 and TLR4 (Ren et al. 2016) on immune cells which induces a predominantly anti-inflammatory response characterized by IL-10 release; this leads immune suppression indicated by decreased monocytic HLA-DR expression and the reduction of TNF-α/IL-6 (Timmermans et al. 2016).

On the other hand, it has been proposed that premature programmed cell death plays a crucial role in the immunosuppressed response after injury and that increased levels of endogenous inflammatory mediators, including HSPs, may activate apoptotic signaling pathways in various innate immune cells (Tschoeke and Ertel 2007). HSPs can contribute to the trauma-mediated immunosuppression through their effects on monocytes as well. Circulating monocytes stimulated by proinflammatory cytokines and presenting antigens are involved in innate and specific immune system responses, and HSP32 (heme oxygenase-1, HO-1) has been suggested to be involved in monocyte-mediated immune response depression in severely ill patients (Mohri et al. 2006). Moreover, it has been shown that HSPA1A inhibited mononuclear cell-derived TNF-α secretion (Luo et al. 2008). Reinforcing the anti-inflammatory properties of HSPA1A, Stice et al. showed that part of its anti-inflammatory activity is due to the inhibition of the expression of proinflammatory transcription factors such as the nuclear factor κβ by blocking the target, activation, and binding (Stice and Knowlton 2008). Therefore, HSPA1A can be proposed as a possible immunosuppressive mediator related to polytrauma. In our former research, parallel to the increase in the serum HSPA1A levels in polytraumatized patients, a significant decrease was seen in the levels of anti-Hsp70 antibodies, and may reflect a part of post-traumatic immunosuppression at the humoral level. The above allows us to presume that HSPs could represent trauma-associated immunomodulatory mediators.

Conclusion

To summarize, IL-6 can be proposed as a potential early predictive marker for systemic inflammatory response, but TNF-α is of little value for predicting injury severity, outcome, or MODS development, and IL-1β is an inefficient parameter and does not therefore warrant inclusion in future studies. Circulating HSPA1A concentrations could serve as a helpful prognostic biomarker early after severe injury, and their quantification may be a valuable predictive tool. Given the role of HSPs in immunosuppression early after severe trauma, monitoring of anti-Hsp70 in the first hours after injury would be a valuable tool for predicting the potential progression of the patient towards immunosuppression. In short, serial quantification of serum HSPA1A and anti-Hsp70 concentrations in the first hours after trauma is proposed as predictive biomarkers of MODS and immunosuppression. This would allow therapeutic and supportive measures to be taken, aimed at reducing sequelae, infections, and other complications, which are responsible for the increase in direct and indirect costs that this type of patient entails for national health systems.

Authors' contributions FC designed and performed the study; MCG wrote the manuscript and analyzed and interpreted the data. JV drafted and revised the manuscript. BA and BB assisted with data presentation, drafting, and critical revision of the manuscript. All authors read and approved the final manuscript.FundingThis work was supported by the Ministry of Economy and Competitiveness ISCIII-FIS grants PI-13/01871, co-financed by ERDF (FEDER) Funds from the European Commission "A way of making Europe."

Compliance with ethical standards

Ethics approval and consent to participate This study was approved by the Hospital General Universitario "Gregorio Marañón" Clinical Research Ethics Committee. All patients or their direct relatives signed consent prior to inclusion in the study.

Consent to publish Not applicable.

Availability of data and materials The data appearing in this review are already publicly available in the literature. The datasets that are used and analyzed for the present study are available from the corresponding author upon reasonable request.

Competing interests The authors declare that they have no competing interests.

References

Asea A (2008). Hsp70: a chaperokine. In: John Wiley & Sons Ltd (eds). The biology of extracellular molecular chaperones. Novartis Found Symp. West Sussex, UK 291:173–9; discussion 221-4

Binkowska AM, Michalak G, Słotwiński R (2015) Current views on the mechanisms of immune responses to trauma and infection. Cent Eur J Immunol 40:206–216

Borges TJ, Wieten L, van Herwijnen MJ, Broere F, van der Zee R, Bonorino C, van Eden W (2012) The anti-inflammatory mechanisms of Hsp70. Front Immunol 3:95

Borges TJ, Lang BJ, Lopes RL, Bonorino C (2016) Modulation of alloimmunity by heat shock proteins. Front Immunol 7:303

Brøchner AC, Toft P (2009) Pathophysiology of the systemic inflammatory response after major accidental trauma. Scand J Trauma Resusc Emerg Med 17:43

Butcher NE, Enninghorst N, Sisak K, Balogh ZJ (2013) The definition of polytrauma: variable interrater versus intrarater agreement–a prospective international study among trauma surgeons. J Trauma Acute Care Surg 74:884–889

Calderwood SK, Mambula SS, Gray PJ Jr, Theriault JR (2007) Extracellular heat shock proteins in cell signaling. FEBS Lett 581: 3689–3694

Chebotareva N, Bobkova I, Shilov E (2017) Heat shock proteins and kidney disease: perspectives of HSP therapy. Cell Stress Chaperones 22:319–343

Cherry RA, King TS, Carney DE, Bryant P, Cooney RN (2007) Trauma team activation and the impact on mortality. J Trauma 63:326–330

Ciriello V, Gudipati S, Stavrou PZ, Kanakaris NK, Bellamy MC, Giannoudis PV (2013) Biomarkers predicting sepsis in polytrauma patients: current evidence. Injury 44:1680–1692

Claridge JA, Golob JF Jr, Leukhardt WH, Sando MJ, Fadlalla AM, Peerless JR, Yowler CJ (2010) The "fever workup" and respiratory culture practice in critically ill trauma patients. J Crit Care 25:493–500

Cuschieri J, Bulger E, Schaeffer V, Sakr S, Nathens AB, Hennessy L, Minei J, Moore EE, O'Keefe G, Sperry J, Remick D, Tompkins R, Maier RV (2010) Inflammation and the host response to Injury Collaborative Research Program. Early elevation in random plasma IL-6 after severe injury is associated with development of organ failure. Shock 34:346–351

De Maio A (1999) Heat shock proteins: facts, thoughts, and dreams. Shock 11:1–12

Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. In American College of Chest Physicians/Society of Critical care medicine consensus conference (1992). Crit Care Med 20:864–874

Dehbi M, Baturcam E, Eldali A, Ahmed M, Kwaasi A, Chishti MA, Bouchama A (2010) Hsp-72, a candidate prognostic indicator of heatstroke. Cell Stress Chaperones 15:593–603

Dekker AB, Krijnen P, Schipper IB (2016) Predictive value of cytokines for developing complications after polytrauma. World J Crit Care Med 5:187–200

DeMeester SL, Buchman TG, Cobb JP (2001) The heat shock paradox: does NF-kB determine cell fate? FASEB J 15:270–274

Demetriades D, Murray J, Charalambides K, Alo K, Velmahos G, Rhee P, Chan L (2004) Trauma fatalities: time and location of hospital deaths. J Am Coll Surg 198:20–26

Dulin E, García-Barreno P, Guisasola MC (2010) Extracellular heat shock protein 70 (HSPA1A) and classical vascular risk factors in a general population. Cell Stress Chaperones 15:929–937

Flohé SB, Bangen JM, Flohé S, Agrawal H, Bergmann K, Schade FU (2007a) Origin of immunomodulation after soft tissue trauma: potential involvement of extracellular heat-shock proteins. Shock 27: 494–502

Flohé S, Flohé SB, Schade FU, Waydhas C (2007b) Immune response of severely injured patients–influence of surgical intervention and therapeutic impact. Langenbeck's Arch Surg 392:639–648

Flohé SB, Flohé S, Schade FU (2008) Deterioration of the immune system after trauma: signals and cellular mechanisms. Innate Immun 14:333–344

Frink M, van Griensven M, Kobbe P, Brin T, Zeckey C, Vaske B, Krettek C, Hildebrand F (2009) IL-6 predicts organ dysfunction and mortality in patients with multiple injuries. Scand J Trauma Resusc Emerg Med 17:49

Frolov A, Yang L, Dong H, Hammock BD, Crofford LJ (2013) Anti-inflammatory properties of prostaglandin E2: deletion of microsomal prostaglandin E synthase-1 exacerbates non-immune inflammatory arthritis in mice. Prostaglandins Leukot Essent Fat Acids 89:351–358

Gallucci S, Matzinger P (2001) Danger signals: SOS to the immune system. Curr Opin Immunol 13(1):114–119

Gerner C, Vejda S, Gelbmann D, Bayer E, Gotzmann J, Schulte-Hermann R, Mikulits W (2002) Concomitant determination of absolute values of cellular protein amounts, synthesis rates, and turnover rates by quantitative proteome profiling. Mol Cell Proteomics 1:528–537

Giannoudis PV (2003) Current concepts of the inflammatory response after major trauma: an update. Injury 34:397–404

Giannoudis PV, Hildebrand F, Pape HC (2004) Inflammatory serum markers in patients with multiple trauma. Can they predict outcome? J Bone Joint Surg Br 86:313–323

van Griensven M (2014) Cytokines as biomarkers in polytraumatized patients. Unfallchirurg 117:699–702

Guisasola MC, Ortiz A, Chana F, Alonso B, Vaquero J (2015) Early inflammatory response in polytraumatized patients: cytokines and heat shock proteins. A pilot study. Orthop Traumatol Surg Res 101: 607–611

Kampinga HH, Hageman J, Vos MJ, Kubota H, Tanguay RM, Bruford EA, Cheetham ME, Chen B, Hightower LE (2009) Guidelines for the nomenclature of the human heat shock proteins. Cell Stress Chaperones 14:105–111

Keel M, Trentz O (2005) Pathophysiology of polytrauma. Injury 36:691–709

Kelly KB, Banerjee A, Golob JF, Fadlalla AA, Claridge JA (2014) Where's the difference? Presentation of nosocomial infection in critically ill trauma versus general surgery patients. Surg Infect 15:377–381

Koliński T, Marek-Trzonkowska N, Trzonkowski P, Siebert J (2016) Heat shock proteins (HSPs) in the homeostasis of regulatory T cells (Tregs). Cent Eur J Immunol 41:317–323

Lamb CM, MacGoey P, Navarro AP, Brooks AJ (2014) Damage control surgery in the era of damage control resuscitation. Br J Anaesth 113: 242–249

Lausevic Z, Lausevic M, Trbojevic-Stankovic J, Krstic S, Stojimirovic B (2008) Predicting multiple organ failure in patients with severe trauma. Can J Surg 51:97–102

Luo X, Zuo X, Zhou Y, Zhang B, Shi Y, Liu M, Wang K, McMillian DR, Xiao X (2008) Extracellular heat shock protein 70 inhibits tumor necrosis factor-alpha induced proinflammatory mediator production in fibroblast-like synoviocytes. Arthritis Res Ther 10:R41

Matzinger P (1994) Tolerance, danger, and the extended family. Annu Rev Immunol 12:991–1045

Matzinger P (1998) An innate sense of danger. Semin Immunol 10:399–415

Mimoz O, Benoist JF, Edouard AR, Assicot M, Bohuon C, Samii K (1998) Procalcitonin and C-reactive protein during the early post-traumatic systemic inflammatory response syndrome. Intensive Care Med 24:185–188

Mohri T, Ogura H, Koh T, Fujita K, Sumi Y, Yoshiya K, Matsushima A, Hosotsubo H, Kuwagata Y, Tanaka H, Shimazu T, Sugimoto H (2006) Enhanced expression of intracellular heme oxygenase-1 in deactivated monocytes from patients with severe systemic inflammatory response syndrome. J Trauma 61:616–623

Namas RA, Mi Q, Namas R, Almahmoud K, Zaaqoq AM, Abdul-Malak O, Azhar N, Day J, Abboud A, Zamora R, Billiar TR, Vodovotz Y (2015) Insights into the role of chemokines, damage-associated molecular patterns, and lymphocyte-derived mediators from computational models of trauma-induced inflammation. Antioxid Redox Signal 23(17):1370–1387

Osterloh A, Breloer M (2008) Heat shock proteins: linking danger and pathogen recognition. Microbiol Immunol 19:1–8

Pape HC, Tsukamoto T, Kobbe P, Tarkin I, Katsoulis S, Peitzman A (2007) Assessment of the clinical course with inflammatory parameters. Injury 38:1358–1364

Pittet JF, Lee H, Morabito D, Howard MB, Welch WJ, Mackersie RC (2006) Serum levels of Hsp 72 measured early after trauma correlate with survival. J Trauma 52:611–617 J Leukoc Biol;79(3):425–34

Pockley AG, Muthana M, Calderwood SK (2008) The dual immmunoregulatory roles of stress proteins. Trends Biochem Sci 33:71–79

Probst C, Pape HC, Hildebrand F, Regel G, Mahlke L, Giannoudis P, Krettek C, Grotz MR (2009) 30 years of polytrauma care: an

analysis of the change in strategies and results of 4849 cases treated at a single institution. Injury 40:77–83

Reikeras O (2010) Immune depression in musculoskeletal trauma. Inflamm Res 59:409–414

Ren B, Zou G, Huang Y, Xu G, Xu F, He J, Zhu H, Yu P (2016) Serum levels of HSP70 and other DAMP proteins can aid in patient diagnosis after traumatic injury. Cell Stress Chaperones 21:677–686

Rizoli S, Nascimento B Jr, Key N, Tien HC, Muraca S, Pinto R, Khalifa M, Plotkin A, Callum J (2011) Disseminated intravascular coagulopathy in the first 24 hours after trauma: the association between ISTH score and anatomopathologic evidence. J Trauma 71(5 Suppl 1):S441–S447

von Rüden C, Woltmann A, Röse M, Wurm S, Rüger M, Hierholzer C, Bühren V (2013) Outcome after severe multiple trauma: a retrospective analysis. J Trauma Manag Outcomes 7:4

Sikand M, Williams K, White C, Moran CG (2005) The financial cost of treating polytrauma: implications for tertiary referral centres in the United Kingdom. Injury 36:733–737

Sousa A, Raposo F, Fonseca S, Valente L, Duarte F, Gonçalves M, Tuna D, Paiva JA (2015) Measurement of cytokines and adhesion molecules in the first 72 hours after severe trauma: association with severity and outcome. Dis Markers 2015:747036

Stice JP, Knowlton AA (2008) Estrogen, NFkappaB, and the heat shock response. Mol Med 14:517–527

Tidball JG (2005) Inflammatory processes in muscle injury and repair. Am J Physiol Regul Integr Comp Physiol 288:R345–R353

Tilg H, Dinarello CA, Mier JW (1997) IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. Immunol Today 18:428–432

Timmermans K, Kox M, Vaneker M, van den Berg M, John A, van Laarhoven A, van der Hoeven H, Scheffer GJ, Pickkers P (2016) Plasma levels of danger-associated molecular patterns are associated with immune suppression in trauma patients. Intensive Care Med 42:551–561

Tschoeke SK, Ertel W (2007) Immunoparalysis after multiple trauma. Injury 38:1346–1357

Vardas K, Apostolou K, Briassouli E, Goukos D, Psarra K, Botoula E, Tsagarakis S, Magira E, Routsi C, Nanas S, Briassoulis G (2014) Early response roles for prolactin cortisol and circulating and cellular levels of heat shock proteins 72 and 90α in severe sepsis and SIRS. Biomed Res Int 2014:803561

Volpin G, Cohen M, Assaf M, Meir T, Katz R, Pollack S (2014) Cytokine levels (IL-4, IL-6, IL-8 and TGFβ) as potential biomarkers of systemic inflammatory response in trauma patients. Int Orthop 38: 1303–1309

Weckbach S, Perl M, Heiland T, Braumüller S, Stahel PF, Flierl MA, Ignatius A, Gebhard F, Huber-Lang M (2012) A new experimental polytrauma model in rats: molecular characterization of the early inflammatory response. Mediat Inflamm 2012:890816

Wirtz MR, Baumann HM, Klinkspoor JH, Goslings JC, Juffermans NP (2017) Viscoelastic testing in trauma. Semin Thromb Hemost 43: 375–385

Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, Hayden DL et al (2011) A genomic storm in critically injured humans. J Exp Med 208:2581–2590

Zhang X, Tanguay RM, He M, Deng Q, Miao X, Zhou L, Wu T (2011) Variants of HSPA1A in combination with plasma Hsp70 and anti-Hsp70 antibody levels associated with higher risk of acute coronary syndrome. Cardiology 119:57–64