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Immune and metabolic alterations following trauma and sepsis – An overview

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Trauma and sepsis are important medical problems of the 21st century that warrant renewed attention. According to the United States Centers for Disease Control and Prevention (CDC), trauma is the leading cause of death among people under the age of 45. Sepsis is a major cause of death following traumatic injuries and infections – with an estimated annual incidence of over 750,000 in hospitalized patients and about 30% mortality rate [1,2].

Over the past four decades there has been a significant increase in the incidence of sepsis mainly attributed to the aging population, whereas traumatic injuries are the major cause of death in the productive age group [3]. Despite advances in medical care, treatment options to significantly reduce the mortality rate following trauma or sepsis have been limited.

The perturbations in metabolic pathways, hypoxic response of the host, and an immune system in overdrive are hallmarks of trauma and sepsis at the molecular level. There is a strong interrelationship between changes in metabolic processes and the immune dysregulation observed in trauma and sepsis, and this immune-metabolic disturbance strongly influences the outcome. This special issue of the journal brings forth current research initiatives in some leading laboratories to better define the metabolic and immunological alterations following traumatic brain injury, burn trauma, polytrauma, hemorrhagic shock and sepsis.

In response to conditions such as hypoxia and nutrient deprivation, one of the first responders is the endoplasmic reticulum, which initiates an unfolded protein response (UPR). Mitochondria, the source of cellular ATP, are also an integral part of this first response [4]. The failure of the mitochondrial defense in critical illness is characterized by increased oxidative stress, impairment of autophagy, and alterations in mitochondrial dynamics. Thiessen, Van den Berghe and Vanhorebeek provide an excellent overview of the role of mitochondrial dysfunction and endoplasmic reticulum stress in critical illness-induced multiple organ failure [5]. According to the authors, “the timing of activating mitochondrial biogenesis during the course of critical illness may be important, since it is metabolically expensive and therefore perhaps not desirable when energy is already scarce, such as in the acute phase of critical illness.” Further, they describe the mitochondrial-glycolytic shift in response to cellular hypoxia and nutrient deprivation as well as the UPR triggered by endoplasmic reticulum in critical illness. The metabolic dysregulation triggered

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as a survival response cannot keep the cellular machinery function in “emergency mode” for a prolonged period of time, thus resulting in organ failure and death.

The need to better understand mitochondrial metabolism and function in trauma and sepsis is increasingly being recognized. The manuscript by Ricchetti and colleagues describes the association of long-term myopathy following sepsis with the failure of skeletal muscle stem cells to regenerate the muscle [6]. They discuss sepsis-induced mitochondrial dysfunction observed in the satellite cells (muscle stem cells) and suggest that mitochondrial impairment in satellite cells may be rescued by treatment with mesenchymal stem cells. The report further highlights the immunomodulatory properties of stem cells and discusses several previous studies that use stem cells in treating experimental models of sepsis.

Caldwell and colleagues report that neutrophil derived microparticles can influence the host response in sepsis induced by cecal ligation and puncture (CLP) [7]. The microparticles can modulate target cell function by interaction with cell surface receptors or intra cellular delivery of the cargo containing bioactive factors such as miRNA. According to the authors, neutrophil-derived microparticles are the most predominant microparticles observed in sepsis [7] and administration of these microparticles into the mice during CLP increased mortality. The authors conclude that neutrophil-derived microparticles augment immune dysfunction in sepsis by inhibiting innate immune response mediated by neutrophils and macrophages.

In a comprehensive review of the role of pattern recognition receptors in trauma and sepsis, Efron and colleagues highlight the significance of both pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPS) in the inflammatory process [8]. They suggest that the interactions between these alarmins and pattern recognition receptors are essential to survival following infection and injury, and may also play a pathologic role in trauma and sepsis. The studies show that in order to develop therapeutics based on the control of inflammatory response in sepsis and trauma, a better understanding of the mechanism by which PAMPS and DAMPS regulate cell function at the molecular level is necessary.

In a comprehensive review of intestinal microenvironment in sepsis, Coopersmith and colleagues describe the changes in structure and function of intestinal barrier with sepsis [9]. They review current concepts with regard to absorptive function as well as the contribution of the microbiome to intestinal homeostasis and consequences of barrier disruption in sepsis. The researchers elaborate how a beneficial microbiome turns into a pathobiome that is deleterious to the host. The pros and cons of targeting the microbiome using methods such as fecal transplant and selective decontamination of the digestive tract are discussed in detail.

Ping Wang and colleagues showed that combined treatment of mice with ghrelin and growth hormone improves immune function in 24 month old septic animals that underwent cecal ligation and puncture [10]. They conclude that co-administration of ghrelin and growth hormone reverses immunosuppression caused by sepsis in the aged population.

Cho and colleagues cloned 64 unique MuERV (Murine endogenous retroviruses) promoters and found up to two glucocorticoid (GC) response elements in each of them [11]. Based upon the results, they suggest that the injury/infection-induced GCs may contribute to inflammatory responses in injury and sepsis, and the response may vary depending on the mouse strain or the genetic makeup of the patient.

Traumatic brain injury (TBI) is a major cause of death and disability and derangement of a complex set of metabolic pathways follow the injury [12]. Oxidative stress, including lipid peroxidation, is widely regarded as an important factor among the complex immune-metabolic response in neurological injury. Using a newly developed global liquid chromatography tandem-mass spectrometry Bayir and colleagues identified over 200 oxidized free fatty acids and monitored their levels up to 24 h following the cortical impact. They found that only anti-inflammatory signals remained elevated at 24 h while the proinflammatory lipid mediators normalized in the contusional cortex after a few hours following the injury. Among the oxidized free fatty acids, 15-lipoxigenase products were the predominant species suggesting a persistent anti-inflammatory process after TBI. The authors conclude that enzymatic lipid peroxidation is the predominant mechanism in oxidative signaling after TBI.

In another article, Dhandapani and colleagues discuss the emerging concept on the possible role of damage associated molecular patterns (DAMPS) in white matter damage following TBI [13]. They provide an overview of recent reports to substantiate the argument that progressive neurological injury is mediated by DAMPS such as HMGB1 (high mobility group box protein 1) and ATP (adenosine triphosphate) after TBI. Their article highlights the need to identify the relationship between immune response and white matter injury following TBI to develop more targeted treatment strategies for these patients. The article by Dhandapani group and the review by Efron and colleagues on the role of DAMPs and PAMPs in injury and infection highlight the significance and the current research trend on the role of these danger signals in trauma and sepsis [8,13].

As seen in the above described reports, the molecular basis of inflammatory response following injury is complex. Nitric oxide (NO) and its derivatives may also act as inflammatory mediators and TBI is known to be associated with elevated levels of nitric oxide (NO) in various organs [14]. NO is a gaseous molecule and its synthesis is catalyzed by nitric oxide synthase (NOS). The three isoforms are: endothelial, neuronal, and inducible NOS. Kozlov et al. reviewed recent studies on the possible mechanisms involved in NO changes following TBI and the mechanisms that alter NO metabolism in the context of TBI [14]. They also discuss remote transport of NO, the role of NO imbalance in TBI-associated glutamate cytotoxicity, and mitochondrial dysfunction following TBI. The mechanistic aspects of NO transport and metabolism are significant towards the understanding of the pathobiology of injury conditions.

A prolonged hypermetabolic state extending several years is triggered following severe burn injury. Jeschke and colleagues describe potential mechanisms of cellular and metabolic dysfunction after burn injury [15]. According to the authors despite the last five decades of research little is known with regard to the factors that contribute to the metabolic

derangement in burn trauma. The article is focused on molecular mediators that play a role in the induction and mediation of the hypercatabolic condition post-thermal injury.

Micro RNA biology is a fast evolving area of study with great potential to advance our understanding of the fundamental basis of functional regulation and to formulate treatment strategies. The manuscript from Choudhry laboratory reports findings on the role of miR-150 in gut inflammation following a combined insult of ethanol and burn injury [16]. Their results show that ethanol and burn injury decreases expression of miR-150 along with the expression of Drosha and Ago-2 in small intestinal epithelial cells. Overexpression of miR-150 in young adult mouse colonic epithelial cells causes a decrease in inflammatory mediators. Together these findings highlight the significance of microRNAs in gut barrier maintenance following ethanol and burn injury.

According to the CDC more than two-thirds of adults are considered obese and obesity is increasing in developing world with improving socio-economic conditions. However, most of the experimental investigations in sepsis are conducted in non-obese animal models. Therefore, considering the significant prevalence of obesity world-wide, models addressing the influence of obesity in sepsis pathogenesis and treatment are very important. Using a CLP model of sepsis, Kaplan and colleagues show that high-fat diets alter myocardial injury following CLP-induced sepsis and that this may be due to changes in cardiac STAT3 signaling [17]. The authors further conclude that there is a dysregulation of compensatory pathways in obese mice hearts in response to sepsis.

In a review article, Dubick and colleagues summarize some of the molecular processes and mechanisms reported to be involved in the development of acute kidney injury after hemorrhagic shock or burn injury based on investigations using animal models [18]. The identification of systemic alterations contributing to kidney injury is important in timely diagnosis and restoring organ function. The report is an exhaustive description of the inflammatory and metabolic alterations associated with acute kidney injury following these traumatic injuries.

Most experimental models of traumatic injuries address single trauma conditions to understand molecular changes associated with the injury in a reductionistic manner. However, polytrauma is a more realistic condition, common in industrial and automobile accidents as well as in modern warfare. Messina and colleagues describe a polytrauma model with combined soft tissue trauma, cecal ligation and puncture, and burn injury [19]. In their original article, a time-dependent increase in hepatic ER stress and insulin resistance following the polytrauma is reported.

Zingarelli and colleagues found an age and gender dependent difference in hemodynamic stability and myocardial damage, with more severity in the aged and the males, following hemorrhagic shock [20]. The impairment was characterized by decreased activation of AMPK and reduced nuclear translocation of PGC-1α. AMPK is an energy sensor and changes in AMPK levels and activity are inter-linked with the cellular energetic status. They further report that targeting metabolic recovery with metformin, an AMPK activator, results in cardioprotective effects after hemorrhagic shock [20].

Raju and colleagues tested oxygen consumption rate in splenocytes isolated from rats following hemorrhagic shock and demonstrated a decline in splenocyte mitochondrial function [21]. They also show an increased inflammatory response in splenocytes of rats subjected to hemorrhagic shock when compared to Sham controls. The mechanisms involved in the decreased mitochondrial function and enhanced inflammatory response in splenocytes as well as the contribution of each of the subsets of splenic immune cells in this process need to be further examined.

In summary, the mechanistic interrelationships and alterations in immune-metabolic pathways in trauma and sepsis are being addressed by several research groups. This special issue is comprised of a combination of original research articles and comprehensive reviews from 17 research laboratories. The contributions demonstrate the increasing focus on understanding the molecular basis of trauma and sepsis. Ongoing studies on stress-induced metabolic dysregulation, the role of mitochondria in cellular energetics, alarmins in immune aberrations, and microparticles and their miRNA cargos in cell-cell communications will advance our fundamental knowledge of trauma and sepsis and help us design better treatment strategies.

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Biography

Raghavan Raju is a Professor of Pharmacology, Biochemistry and Molecular Biology, and Surgery in the Medical College of Georgia in Augusta University (formerly Georgia Regents University). Dr. Raju's research is focused on hemorrhagic shock and sepsis. Dr. Raju received his Ph.D. degree from the All India Institute of Medical Sciences in New Delhi and completed his postdoctoral training at the University of Minnesota and Mayo Clinic, Minnesota. He served as a Senior Staff Fellow at the National Institutes of Health and moved to the University of Alabama at Birmingham as an Associate Professor. Dr. Raju joined Augusta University in 2013, where he is a tenured Professor. He is a member of the Shock Society, American Heart Association, American Association of Immunology, and Society for Neuroscience. From 2002 to 2006 he was an Associate Editor of Journal of Immunology and he is currently on the editorial board of BBA-Molecular Basis of Disease, PLOS One, and Aging and Disease. He has published over 65 articles in peer-reviewed journals. Dr. Raju has participated in several grant review panels for the U.S. Federal Government and other agencies including the American Heart Association. Currently, he serves as a chartered member of the NIH study section, Aging Systems and Geriatrics (ASG). His research is funded through grants from the National Institutes of Health.