SEPSIS, SEPTIC SHOCK AND MULTIPLE ORGAN DYSFUNCTION SYNDROME: SELECTED CELLULAR IMMUNE MECHANISMS AND METHODOLOGICAL ASPECTS

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ABSTRACT

Sepsis and septic shock with multiple organ dysfunction syndrome are frequent life-threatening conditions. Despite long-time scientific effort, their exact pathophysiology, causal treatment, and prevention remain obscure. The numbers of mediators and elements (e.g. leukocytes, thrombocytes, endothelium/microcirculation etc.) have been suggested as key mediators in the process of initiation and modulation of this dreadful disease. The aim of the thesis is to better describe and document the cellular mechanisms in the pathophysiology of sepsis, septic shock and multiple organ dysfunction syndrome using different analytic methods including microcirculation assessment, flowcytometry, and proteomics.

The first original manuscript studied the role of neutrophils in the process of microcirculation impairment in septic shock patients, as a central pathophysiological mechanism of systemic inflammation. The real-time intravital videomicroscopy technique was used. This is the first clinical study reporting microvascular changes in septic shock patients with chemotherapy-induced cytopenia. The microcirculation injury was identical in cytopenic compared to non-cytopenic septic patients, suggesting neutrophils – the pivotal elements of immune response – might not be the determining elements alone in this pathophysiological process. Moreover, association of chemotherapy-induced cytopenia without sepsis with significant alteration of sublingual microcirculation was surprising and yet unpublished as well.

The next study was aimed to characterize the role of platelets and dynamics of their phenotype changes in septic shock patients. Multifactorial analysis revealed their significant activation together with alteration of their aggregation and secretion very early in the septic shock. The complex evaluation of the thrombocytes in such clinical setting was applied. The alteration of α-granules content was detected. These changes could reflect alterations at the level of megakaryocytes in the bone marrow. Simultaneously, extranuclear pathways of the synthesis of new functional proteins with consequent phenotype changes of platelets could not be excluded.

Next, clinically relevant experimental study in large animals (piglets) was aimed to analyze dynamic changes in plasma proteome during an early phase of septic shock. Differential proteomic analysis identified a number of unique peptides, and described the dynamics of their plasmatic concentrations. To the best of our knowledge, such findings were published for the first time.

The last original study utilized proteomic analysis to assess proteins bound on both adsorption units of the extracorporeal liver replacement (support) method (Prometheus™). For the first time, surprisingly broad spectrum of such proteins was identified.

Three review articles are integral parts of this thesis. They describe current knowledge of immune response, its mechanisms, and components including neutrophils and platelets, and role of proteomics in the study of these issues.

Keywords

Sepsis – organ dysfunction – pathophysiology – neutrophils – thrombocytes – microcirculation – proteomics