LBI Trauma

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Final Summary Report

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Sepsis mortality remains a significant problem despite extensive investigative efforts and multiple, large scale clinical trials with immunomodulators. Currently, there is no FDA-approved treatment specifically directed against sepsis after the activated recombinant protein C (Xigris®) was withdrawn from the market due to a relatively low effectiveness and serious side effects. Sepsis is a major life-threatening condition in acute-care patients accounting for thousands of deaths annually, despite rapid progress in health care over the past decades in developed countries. Sepsis-related hospital mortality has ranged from 25% to 80% worldwide over the last few decades, reaching 44 deaths per 100,000 population in the United States (US) alone. Sepsis is also frequent in the European Union (EU) with 79,000 cases occurring in Germany/Austria annually (54-116 per 100,000) and ranges there as the third most frequent cause of death.
From a pathological standpoint, sepsis is a complex syndrome with wide presentation of symptoms, hence it is difficult to define, diagnose and treat. A better understanding of the basic immune alterations occurring in sepsis is imperative to devise a targeted and successful therapy against this disease. This project aimed at delineating the nature of some of those derangements.

Specifically, the project addressed the mechanisms and prevention of early mortality in experimental sepsis. The project consisted of three aims investigating acute immuno-inflammatory signaling triggered by a septic event. The aims were formulated to allow better characterization and understanding of the systemic and central nervous system immuno-inflammatory responses preceding death in polymicrobial acute sepsis – all to improve survival by modulating selected genomic/humoral/cellular inflammatory pathways. All three objectives were investigated in a clinically relevant mouse model of abdominal sepsis.

The IRG contained following objectives:

A- To compare organ dysfunction in surviving vs. dying mice in acute polymicrobial sepsis.

B- To determine cytokine gene/protein expression patterns and neurotransmitter changes in brain regions during sub-lethal and lethal sepsis.

C- To determine the effectiveness of individually tailored immuno-modulatory intervention during the acute polymicrobial sepsis.

Given the intangible role of multiply organ failure as a contributor of death in early (acute) septic deaths, we extensively studied this pathophysiological aspect. Interestingly, our experimental data defy the current consensus by indicating that early septic deaths are not directly associated with an overt organ dysfunction. This was especially striking regarding the most common complication encountered in septic patients: severe lung dysfunction. Our studies demonstrated that acute deaths from sepsis were not related to lung failure. This discrepancy may reflect the dissonance between elderly septic patients (most frequently affected by sepsis syndromes) and young age of animal models. Additional experiments are necessary to clarify the role of age in the context of organ component in acute and chronic septic outcomes.

Septic encephalopathy is frequent in patients but it is heavily under diagnosed and its pathophysiology is enigmatic. In order to properly approach this technically challenging study, we established a fruitful cooperation with outside partners (pharm-analyt.at and Vet. University of Vienna). This step combined sophisticated experimental approaches with state-of-the-art detection/evaluation measures. We studied expression of several neurotransmitters and

inflammatory cytokines, and integrity of blood brain barrier (BBB) in selected brain regions during acute sepsis. Septic deaths were preceded by a much stronger deregulation of brain amine metabolism and expression of cytokine response. Yet, these disparities were not universal but it was apparent in selected brain regions and for selected neurotransmitters only. Remarkably, analyses of blood-brain-barrier (BBB) integrity revealed that there were no differences in the leakage between severe and mild cases of sepsis. Similarly, the overall severity-independent comparison revealed that BBB integrity was only minimally compromise during acute phase of sepsis.

We have generated most interesting results in the area of individually tailored immuno-modulatory interventions. First, with our American partner (U. of Boston School of Medicine) we demonstrated that therapy with glucocorticoids (i.e. dexamethasone, an unspecific anti-inflammatory drug) can be successful when given to a narrow, most severely sick cohort of septic subjects, while it appears detrimental when administered to animals whose immune defense system successfully copes with the disease. Another successful cooperation with a UK partner (the William Harvey Research Institute, London) resulted in a promising pre-clinical life-saving intervention study with another anti-inflammatory therapeutic, peroxisome proliferator-activated receptor (PPAR) beta/delta significantly improved survival in acutely septic mice. Most recently, again by means of targeted experimental treatment aimed at narrow, pre-defined septic cohorts, we demonstrated that restoration of fibrinolysis in acute septic is life-threatening. Notably, this observation was not possible after treating the all-inclusive population – it was revealed only after maximally accurate separation of septic subjects into homogenous cohorts based on their risk of death prior to the administration of the drug [anti- Plasminogen Activator Inhibitor 1(PAI-1) antibody]. Again, the success of the latter study was in large part possible thanks to another partner, Catholic University of Loeven, Belgium.

Design of this project focused on effective implementation of the "from bench to bedside" philosophy. Overall, the data generated during the project has filled out a number of gaps in understanding in pathophysiological process that lead to death in early sepsis. Additionally, our targeted pre-clinical data aid in design and creation of pointed weapons needed to improve survival of septic patients. Specifically, our findings reinforce the notion that new drugs against sepsis should be offered selectively to carefully pre-defined narrow cohorts of septic patients who have the best chance to benefit. Such tactics have another great advantage – it may spare life of septic subjects whose fragile immuno-inflammatory defence balance could be worsened by unnecessary treatments, as shown in our most recent study with PAI-1 inhibitor.