SEPSIS: INTEGRATING BASIC RESEARCH AND CLINICAL INVESTIGATION

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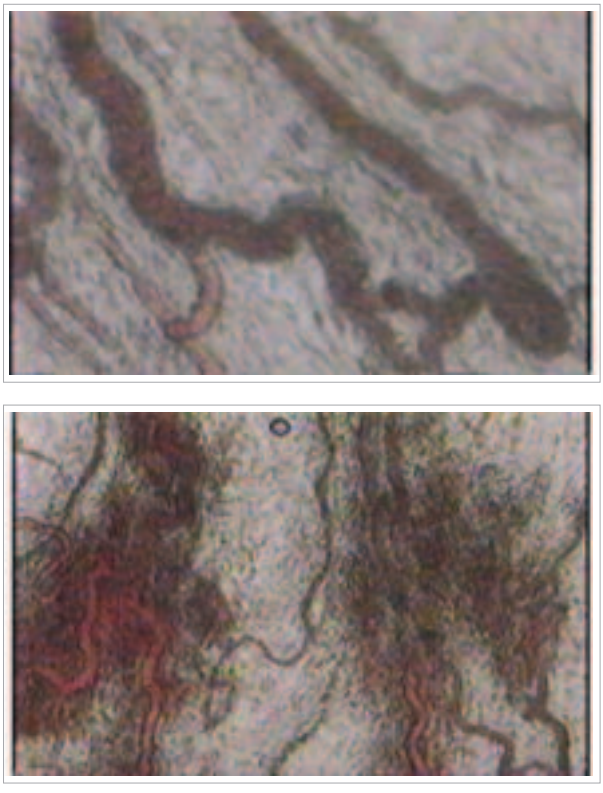

Mesenterial microcirculation two hours after bacterial translocation. Above, SHAM. And below, bacterial translocation

In spite of our best efforts, one out of two patients with severe sepsis and septic shock will still die. Thus, every one of us managing septic patients will be daily faced with the limits of our knowledge and intervention strategies, presenting us with a significant challenge for developing and improving patient care.

In this context, our research will be based on three interrelated lines of investigation:

Clinic and epidemiology.

The primary objective is to identify the main factors, both constitutive and related to therapeutic interventions, which are related to outcomes. The constitutive study will focus on genetic polymorphisms, whereas therapeutic interventions will focus on resuscitation, antimicrobial appropriateness, and support for organ dysfunction. The time elapsed to the correct intervention will be assessed to evaluate the time-dependent interventions. Samples obtained from these patients will be used for functional studies.

Translational Research – cellular response in patients with sepsis.

Cellular response to LPS is modulated during clinical sepsis, yet the mechanisms are only partially understood. The main objective is to evaluate the cellular response across the clinical continuum of sepsis. This includes cell surface expression, cytokine production, ROS generation and evaluation of the TLR pathway genes in PBMC and neutrophils in patients with sepsis, severe sepsis and septic shock.

Experimental models of sepsis.

Bacterial translocation is assumed to play an important role in severely ill patients with sepsis. The objectives are to evaluate the effects of bacterial translocation from gut in the modulation of inflammatory response in blood and in the lymph. The combination of systemic infection and bacterial translocation will be assessed regarding lethality, microcirculation alterations, and cellular functions in lymph and blood compartments.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Our findings confirm the downregulation of inflammatory cytokines seen in severe sepsis and septic shock, and add evidence of an upregulation in earlier stages of sepsis, which may be related to pathogen recognition because it is more pronounced for LPS than for IL-1β, and TNF-α. In contrast, the downregulation observed in patients with severe sepsis and septic shock appears to be related to intracellular pathways common to LPS, IL-1β, and TNF-α.

Neutrophils and monocytes are activated in patients with sepsis, severe sepsis and septic shock considering oxidative metabolism. In the onset phase of sepsis, increased oxidative metabolism may be beneficial and is probably involved in resolution of the infectious course, but the persistence of high oxygen species formation in later stages may be associated with tissue damage and consequently organ dysfunction and death.

Our results show that the expression of TLR signaling pathway genes seems to be differently modulated in monocytes and neutrophils in patients with sepsis, severe sepsis and septic shock. Mononuclear cells presented downregulation in septic shock, predominantly in NFKB pathway, confirming the immunosuppressive nature of septic shock patients. On the other hand, neutrophils show predominantly upregulated genes, which comprise differential gene groups persistently upregulated across the stages of sepsis.

MAIN PUBLICATIONS

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