Emerging Concepts In The Pathophysiology Of Acute Pancreatitis

Anubhav Mittal

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Abstract

There is no specific treatment for acute pancreatitis (AP) reflecting an incomplete understanding of the critical pathophysiological factors that determine severity, drive multiple organ dysfunction (MODS) and cause the high mortality. New treatment paradigms are needed, and this thesis explores three paradigms that may offer novel approaches to severity assessment and treatment.

Patients with acute pancreatitis are prone to hypotension and oxidative stress. Cyclic voltammetry (CyV) was adapted to measure serum redox status during both experimental AP and shock. CyV was found to accurately reflect disease severity. Clinical trials are now needed to demonstrate the feasibility and utility of this approach at the bedside for real-time monitoring of the antioxidant capacity of patients and response to resuscitation.

There is preliminary evidence to suggest that MODS might be mediated by toxic factors in the protein fraction of disease conditioned mesenteric lymph (ML). Using the advanced proteomic techniques of isobaric tags (iTRAQ™) for relative protein quantitation together with liquid chromatography–tandem mass spectrometry for the identification of the component proteins, the first comprehensive description of the normal (fasted and fed) rodent ML proteome is provided in this thesis. This was followed by separate studies to define ML proteome in AP and systemic shock. A bioinformatics approach was applied to identify key pathways and significant protein-protein interactions.

The relatively new concept of cytopathic hypoxia has not been investigated in AP, even though mitochondrial dysfunction (MD) plays a key role in the development of MODS. Here, it was shown that significant MD was present, as expected, in the pancreas and lung, but also in the jejunum early in AP. These findings justify the further investigation of mitochondrial specific therapies in AP.

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