Cytokine storm in acute pancreatitis

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Abstract Efforts to unravel the events in the evolution of tissue damage in acute pancreatitis have shown a number of inflammatory mediators to be involved. The pathways of damage are similar, whatever the etiology of pancreatitis, with three phases of progression: local acinar injury, systemic response, and generalized sepsis. The proinflammatory response is countered by an anti-inflammatory response, and an imbalance between these two systems leads to localized tissue destruction and distant organ damage. Cytokines lie at the heart of the problem and are involved in all aspects of the cascade leading to systemic inflammatory response syndrome and multiple organ dysfunction syndrome. This review discusses the present knowledge about the role of various mediators in this process, their genetic control, and the effects of their modulation. The major proinflammatory mediators are tumor necrosis factor, interleukins 1, 6, and 8, platelet activation factor, and the chemokines. The major anti-inflammatory factors include interleukin 10, and interleukin 1 receptor antagonist. Emerging knowledge of new mediators as well as future strategy of damage control is discussed.

Key words Acute pancreatitis · Cytokine · Macrophage · Interleukin-1 · Tumor necrosis factor

Introduction

Acute pancreatitis (AP) is a commonly encountered intra-abdominal catastrophe and is a world-wide problem. At the present time, no specific therapy has been shown to be uniformly effective in reducing the mortality, or indeed, the morbidity resulting from it. The current principles of treatment of AP remain the same as in the previous century, using supportive therapy. The constituents of supportive therapy have undergone a number of refinements; however, as yet, there is no treatment that can downregulate the powerful inflammatory processes.

The epidemiological data reveal the incidence of AP to vary from 48 to 238 cases per million population. Of these cases, severe AP accounts for about 10%–25%, with the overall mortality from AP remaining at about 9%–20% over the past few decades. Of the patients who die, 60% do so within the first 6 days following admission, and the major cause of death, among them, is pulmonary complications such as adult respiratory distress syndrome (ARDS). The majority of deaths after the first week are from infectious causes such as infected pancreatic necrosis and septicemia. The two common causes of AP are gallstones, accounting for 40%–50% of cases, and ethanol, which accounts for around 20%–30% of cases. About 10% of cases have a diverse etiology, such as hyperlipidemia, viral infection, drugs, hypercalcemia, and ductal obstruction.

After the initial injury to the pancreatic acinar cell, whatever the triggering factor, events take a similar path for all patients with AP. The disease progression can be viewed as a three-phase continuum: local inflammation of the pancreas, a generalized inflammatory response, and the final stage of sepsis, with multiple organ damage. The disease process can extend to any of the three phases, and is often resolved after the local inflammatory process, resulting in mild AP. After the initial pancreatic acinar cell injury, inflammatory cells adhere to the endothelium due to the expression of various adhesion molecules, such as vascular cellular adhesion molecule-1 (VCAM-1) and P- and E-selectins, etc. This propagates an exponentially increasing response which occasionally spirals out of control to give rise to severe AP and terminates in death.

Key cells involved in elaborating the inflammatory mediators are the pancreatic acinar cells, the endothelial cells, neutrophils, lymphocytes, and the macrophages/monocytes. A variety of inflammatory mediators of different chemical and functional classes
are elaborated in the inflammatory process, such as arachidonic acid metabolites, nitric oxide, cytokines, and reactive oxygen species. These elicit responses resulting in increased vascular permeability, modulation of leukocyte trafficking, localized tissue destruction, and generalized inflammation, with damage to kidney, lung, and various other organs. The initial clinical response to pancreatitis is a systemic inflammatory response (SIRS), which, if abnormally persistent, develops into a worsening scenario of tissue damage and sepsis resulting in multiple organ dysfunction syndrome (MODS).9 The spectrum of inflammatory responses of the body has been further studied in the past few years. These responses vary from SIRS that can progress on to MODS or take the more indolent form of a compensatory anti-inflammatory syndrome (CARS).9 The current understanding is that SIRS is the proinflammatory response and CARS is the anti-inflammatory response that results in a prolonged period of depressed immune function and increased susceptibility to infections.10 The initial SIRS cascade occurs over the first week of illness and its resolution is the crucial step in deciding the further course of events. The primary mediators of this process are the cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-8 (IL-8), among others (Fig. 1). The pro-inflammatory process is counterbalanced by the anti-inflammatory response that inhibits T-cell mitogenesis and decreases cytokine production.

**Cytokines: in the eye of the storm**

The cytokines are a family of low-molecular weight proteins (16–25kDa) that are secreted by a multitude of cells. They are usually not found in normal tissue but are produced in response to stimuli via receptor-induced pathways. Cytokine secretion is a very closely