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Salvaging the septic heart through targeting the IL-6/p38 MAPK signaling network

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Keywords

Sepsis; myocardial dysfunction; IL-6; p38 MAPK; MK2

Depression of myocardial function during severe sepsis, which currently accounts for approx. 200,000 deaths/year in the United States (1), is characterized by a decrease in contractility and a poor response to fluid therapy (2). Since the md-1980s it has been recognized that the decreased cardiac function, which undoubtedly contributes to the overall pathophysiology of the septic state, does not arise from factors that are intrinsic to the myocardium, but instead results from the presence of circulating myocardial depressant factors (3, 4). Since much of the massive inflammation and multi-organ dysfunction in sepsis result from the secretion of various cytokines, it was long suspected that these proteins were also responsible, at least in part, for the observed myocardial dysfunction, although their identification, and the molecular basis for their effects on myocyte function were poorly understood.

Pathan and colleagues recently showed that the cytokine IL-6 is a major factor responsible for modulating myocardial depression in children with meningococcal septicemia (5). In this issue of Critical Care Medicine, Pathan et al., use an in-vitro cardiac myocyte cell culture system to investigate the signaling pathways (and potential drug targets) that modulate and/or are modulated by IL-6 (new article). They report that the stress activated p38 mitogen activated protein kinase (p38 MAPK) pathway controls IL-6-induced myocardial depression and that this can be reversed using a specific chemical inhibitor of this kinase (SB203580). The authors go on to look at gene expression changes in a small cohort of pediatric patients with meningococcal sepsis and find a number of differences between septic patients and healthy controls. Amongst the genes that show differential expression are a number of upstream and downstream regulators of p38 MAPK signaling indicating that this pathway is deregulated in this cohort of patients. However, the mechanism by which such a large group of genes involved in p38 MAPK signaling could be deregulated remains to be determined. In addition to the work of Pathan et al., are a number of observations that link p38 MAPK and one of it's downstream kinases, MK2 (MAPKAPK2) to the control of IL-6 biosynthesis (6). For example, during LPS-induced inflammation p38 MAPK activates MK2, which in turn controls IL-6 production by stabilizing the IL-6 messenger RNA (7). Therefore the p38

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MAPK/MK2 pathway appears to lie both upstream and downstream of IL-6 in inflammation and sepsis.

These observations are of obvious clinical relevance since p38 MAPK and its downstream effectors are under intense scrutiny as viable drug targets for the treatment of a number of diseases from colitis to cancer (6, 8, 9). The current study further highlights the potential utility of p38 MAPK inhibitors in the specific management of sepsis-associated cardiac dysfunction. p38 MAPK, however, activates a variety of downstream effectors that affect a wide variety of other cellular responses during sepsis in addition to cytokine secretion and myocardial contractility, including effects on apoptosis and neutrophil function (10, 11). In this regard, drugs that target the specific components of the p38 MAPK pathway that are central to its IL-6 effects, such as MK2 or its substrates, may also show promise in the clinical treatment of sepsis by preventing IL-6 production thus inhibiting myocardial depression, while having fewer effects on other p38 MAPK-dependent responses. In this regard emerging new drugs targeting IL-6 itself, such as IL-6 blocking monoclonal antibodies (12), may also show utility in this setting. Importantly the utility of these drugs will not be limited to myocardial dysfunction in sepsis since the p38 MAPK/MK2/IL6 pathway appears to be a major determinant of response to chemotherapy in certain cancers (13, 14). For example, p38 MAPK-dependent IL-6 secretion from thymic endothelial cells mediates drug resistance and relapse in a mouse model of Burkitt's lymphoma (15). Therefore new drugs targeting the p38 MAPK-MK2-IL-6 signaling pathway may have a broader utility in cancer treatment as well as for the treatment of conditions where chronic inflammation is a major driving force of the diseased state, such as sepsis. If such drugs prove useful, it will be yet another example of how agents that were developed to limit the pathology of inflammation, such as cyclooxygenase inhibitors, can have a double life in clinical oncology. That indeed would be quite a lot of heart to salvage.

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