

Contributions to inflammation and sepsis by Inhibitor of Apoptosis proteins

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Abstract

Sepsis is a significant clinical challenge that is increasing in incidence and carries a substantial risk of mortality. The syndrome is characterized by vasodilation, vascular permeability and hypoperfusion that leads to disseminated intravascular coagulation and acute organ dysfunction in severe cases. These manifestations are attributable to an overly zealous host innate immune response that causes a systemic pro-inflammatory state, and apoptosis of both immune cells and non-immune cells has been implicated in the pathogenesis of sepsis.

The primary focus of this dissertation investigates the connection between molecular regulation of apoptosis and inflammation, specifically focusing on the role of that anti-apoptotic protein c-IAP1 (cellular Inhibitor of Apoptosis 1), a member of the Inhibitor of Apoptosis (IAP) family. We identified a novel role for c-IAP1 during pathologic innate immune responses that result in septic shock, using mouse models of sepsis. During sepsis c-IAP1-deficient mice demonstrated improved survival, and we identified a contribution of c-IAP1 to production of systemic cytokines during pro-inflammatory immune responses *in vivo*. While cytokine induction by the gram-negative bacterial product lipopolysaccharide (LPS) was not dependent on c-IAP1 in innate immune cells, we identified a role for c-IAP1 in the response of lung fibroblasts to pro-inflammatory stimuli, including LPS, tumor necrosis factor (TNF) and macrophage-derived cytokines. Lung fibroblasts responded to macrophage-derived TNF in a c-IAP1-dependent manner; however, NF- κ B and MAPK signaling were intact in c-IAP1-deficient fibroblasts and macrophages.

These results indicate that c-IAP1 is a critical pro-inflammatory mediator of innate immune responses during septic shock and implicate c-IAP1 in regulation of the participation of fibroblasts in cytokine networks with immune cells during inflammation. Interconnections between apoptosis and inflammatory processes mediated by IAPs are a potential mechanism to coordinate the sensitivity of the cellular suicide program and adaptation to inflammation in the extracellular environment. Characterization of the integrated regulation of inflammation and apoptosis during pathologic systemic inflammation will improve our understanding of the pathogenesis of sepsis and aid in the development of new therapeutic approaches.

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