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AHPBA Research Award

Title: Regulation of Acute Pancreatitis by C-type Lectin Receptors (Physiology/Biology)

Research Synopsis:

My laboratory studies the role of the innate immune system in pancreatic and liver inflammation as well as in carcinogenesis. We have previously shown that blockade of certain pattern recognition receptors (PRRs), in particular, Toll-Like Receptors 4 and 7 (TLR4 and TLR7), mitigates pancreatic inflammation and the progression to pancreatic cancer. My research focuses on the importance of Mincle, a novel PRR, in the above disease processes. The Mincle receptor is present on many different antigen-presenting cells (APCs), and has been shown to be critical for the immune response to mycobacteria and fungi. However, its role in models of pancreatic inflammation has never been studied.

I have found that Mincle and its signaling intermediates are upregulated in a mouse model of acute pancreatitis. In addition, Mincle blockade decreases pancreatic immune infiltrate. Most significantly, I have discovered that Mincle and TLR4 co-associate on the cell surface, and that Mincle^{-/-} mice have an increased response to TLR4 stimulation. These data suggest that Mincle negatively regulates TLR4 signaling. Regulation of TLR responses is extremely important in maintaining physiologic homeostasis and in limiting septic injury, tissue damage, and autoimmunity. My work seeks to elucidate the cellular mechanism of Mincle and TLR4 cross-talk and its importance in the pathogenesis of pancreatic inflammation. Knowledge of this interaction can ultimately lead to the development of therapeutic interventions for pancreatitis and pancreatic cancer.