Systemic inflammation during acute pancreatitis is regulated by NLRP3 inflammasome activation in pancreatic macrophages

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Introduction: Systemic inflammation in acute pancreatitis determines disease severity and mortality. Macrophages are the dominant infiltrating immune cell population during acute pancreatitis and play a crucial role in immune regulation. We investigated the role of the NLRP3-inflammasome-IL1β/IL18 signaling for the systemic immune response and the disease severity in acute pancreatitis.
Methods: Bone marrow derived macrophages were isolated from C57BL6 mice and co-incubated with freshly prepared acinar cells. Transcriptome analysis of macrophages was performed by affymetrix chip array. Severe acute pancreatitis was induced by partial duct ligation and additional caerulein stimulation (50µg/kg/bodyweight). MCC950 a small molecule inhibitor was used to prevent inflammasome activation *in vivo* as well as *in vitro*. Disease severity was determined by serum amylase, lipase and histology. Systemic inflammation was measured by MPO in the lungs and FACS analysis of splenic leukocyte populations.
Results: Macrophage activation by acinar cells leads to a massive pro-inflammatory immune response and the release of pro-inflammatory cytokines. Activation of the NLRP3 inflammasome complex results in caspase 1 activation and the release of IL1β and IL18. Absence of inflammasome activation by genetic deletion or inhibition via MCC950 results in decreased disease severity and reduced local and systemic inflammation. The pro-inflammatory immune response was triggered not only by innate immunity but activation of the adaptive immune system as splenic CD4+ T-cells were also decreased. Affymetrix chip data from macrophages and acini in co-culture suggest that IL18 is the link to T-cell activation and SIRS.
Conclusion: NLRP3 Inflammasome activation within infiltrating macrophages induces systemic hyperinflammation by activation of the innate and adaptive immune system. Treatment with MCC950 prevents systemic hyperinflammation and decreases pancreatic damage. Inhibition of the inflammasome appears a promising therapeutic option for the treatment of severe acute pancreatitis.