

# NLRP3 Inflammasome activation in macrophages regulates systemic inflammation and severity during acute pancreatitis.

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## Introduction:

The severity and mortality of acute pancreatitis is determined by its systemic inflammatory response. Inflammasome activation by damage-associated-molecular-patterns (DAMPs) could play a crucial role for disease severity. Here we investigated the role of the NLRP3 inflammasome in macrophages during the course of pancreatitis.

## Methods:

Mild pancreatitis was induced in NLRP3<sup>-/-</sup> by hourly intraperitoneal injections of caerulein (50µg/kg bodyweight). Severe necrotizing pancreatitis was induced by partial duct ligation with additional caerulein stimulation. Inhibition of NLRP3 inflammasome was achieved with MCC950. Disease severity was determined by serum amylase, lipase and histology. Systemic inflammation was measured by MPO in lung and FACS analysis of leukocyte activation in spleen. Inflammasome activation was measured in bone marrow derived macrophages co-incubated with acinar cells and on transcription level by affymetrix chip analysis.

## Results:

Macrophages phagocytose dying acinar cells *in vitro* which leads to a massive release of cytokine and a shift to a pro-inflammatory phenotype of cells (M1-like). The inflammasome complex is activated in macrophages and leads to the activation of caspase 1 and the secretion of mature IL1β. Absence of inflammasome activation by genetic deletion or administration of MCC950 results in decreased disease severity in both models of pancreatitis paralleled by less local and systemic inflammation. Affymetrix chip data from macrophages and acini in co-culture suggest that IL18 is the link to SIRS.

## Conclusion:

Inflammasome activation within macrophages induces systemic hyperinflammation *in vivo* as well as *in vitro*. Therapeutic inhibition of inflammasome activation decrease systemic and local damage and is a promising treatment option for severe acute pancreatitis.