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# IL4/IL13 STAT6 Mediated Macrophage Polarization During Acute and Chronic Pancreatitis

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**Abstract :** Aim: Acute pancreatitis (AP) and chronic pancreatitis (CP) are both accompanied by a prominent immune response which influences the course of disease. Whereas during AP the pro-inflammatory immune response dominates, during CP a fibroinflammatory response regulates organ remodeling. The transcription factor signal transducer and activator of transcription 6 (STAT6) is a crucial part of the Type 2 immune response. Here we investigate the role of STAT6 in a mouse model of AP and CP. Material and Methods: AP was induced by hourly repetitive i.p. injections of caerulein (50µg/kg/bodyweight) in C57Bl/6 J and STAT6-/- mice. CP was induced by repetitive caerulein injections 6 times a day, 3 days a week over 4 weeks. Disease severity was evaluated by serum amylase/lipase measurement, H&E staining of pancreas. Pancreatic infiltrate was characterized by immunofluorescent labeling of CD68, CD206, CCR2, CD4 and CD8. Pancreas fibrosis was evaluated by Azan blue staining. qRT-PCR was performed of Arg1, Nos2, Il6, Il1b, Col3a, Socs3 and Ym1. Affymetrix chip array analyses were done to illustrate the IL4/IL13/STAT6 signaling in bone marrow derived macrophages. Results: AP severity is mitigated in STAT6-/- mice, as shown by decreased serum amylase and lipase, as well as histological damage. CP mice surprisingly showed only slightly reduced fibrosis of the pancreas. Also staining of CD206 a classical marker of alternatively activated macrophages showed no decrease of M2-like polarization in the absence of STAT6. In contrast, transcription profile analysis in BMDM showed complete blockade of the IL4/IL13 pathway in STAT6-/- animals. Conclusion: STAT6 signaling pathway is protective during AP and mitigates the pancreatic damage. During chronic pancreatitis the IL4/IL13 – STAT6 axisis involved in organ fibrogenesis. Notably, fibrosis is not dependent on a single signaling pathway, and alternative macrophage activation is also complex and involves different subclasses (M2a, M2b, M2c and M2d) which could be independent of the IL4/IL13 STAT6 axis.

**Keywords :** chronic pancreatitis, macrophages, IL4/IL13, Type immune response
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