Macrophage-specific deletion of *Smad7* does not exacerbate fibrosis after experimental chronic pancreatitis

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Conclusion: Targeting Smad7 in macrophages resulted in a mild protective effect during chronic pancreatitis development.

Introduction

Macrophages are highly involved in different pathogenic phases during chronic pancreatitis (CP) development, including inflammation initiation and resolution, tissue repair and regeneration. However, the underlying mechanism networks remain elusive due to the dynamic and flexible nature of macrophages.

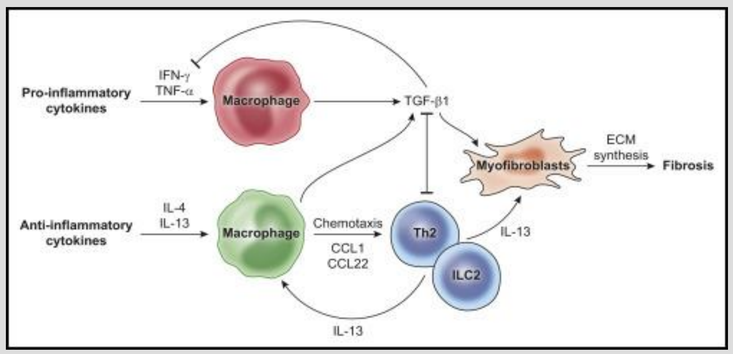


Figure cited from "Macrophages in Tissue Repair, Regeneration, and Fibrosis, PMID:26982353"

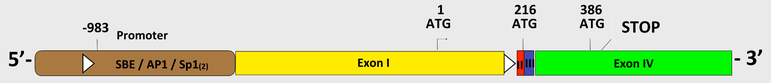
Transforming growth factor beta (TGF-β), mainly produced by macrophages during CP, not only plays a crucial role in pancreatic fibrogenesis through canonic Smad signalling but also affects the phenotype of macrophages.

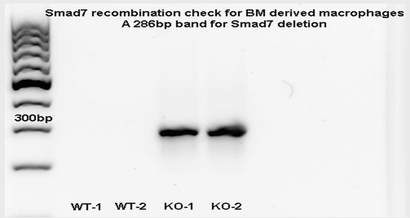
Aims

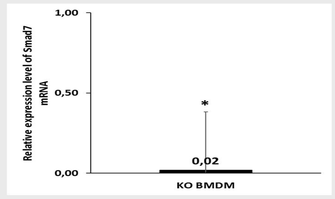
To investigate the role of TGF-β signaling inhibitor Smad7 during macrophage mediated CP development.

Methods and results

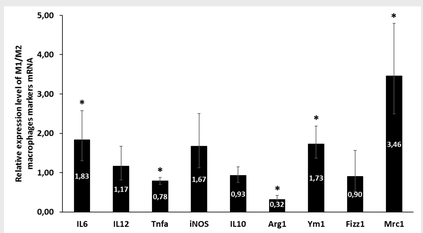
LysM-Cre;Smad7$^{fl/fl}$ (KO) mice were used to generate a macrophage-specific Smad7 deletion. Repeated cerulein injection was used to induce CP.

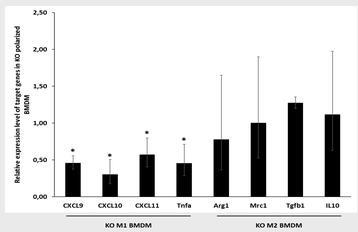




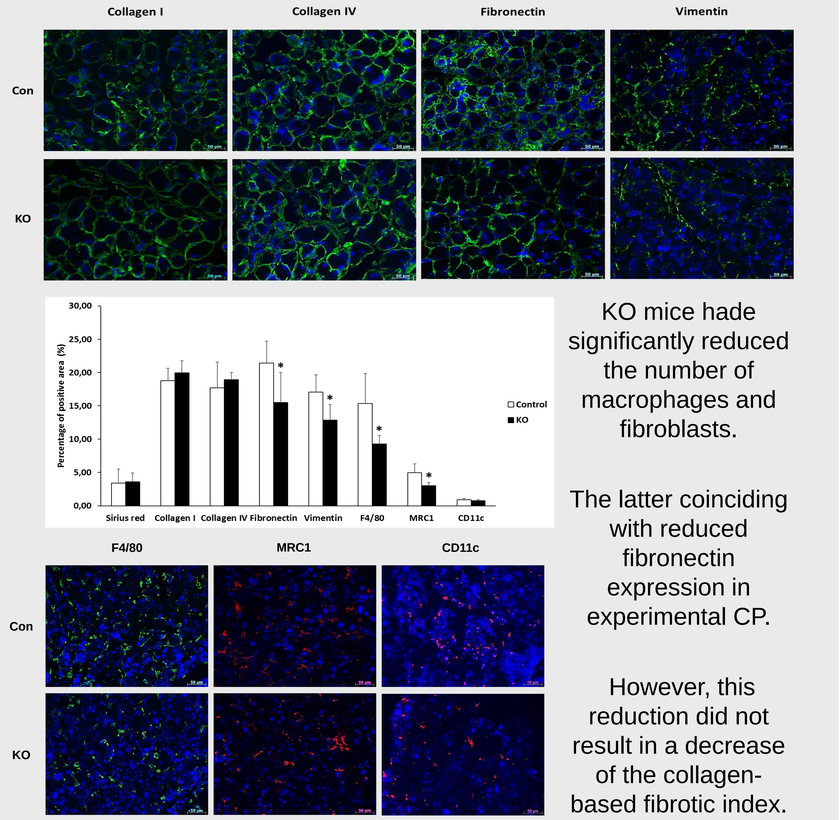


Primary pancreatic stellate cells (PSCs) were isolated from *Col1a2-Cre^{ERT}-tdTomato* mice, and bone marrow-derived macrophages (BMDM) were isolated from *LysM-Cre; Smad7$^{fl/fl}$* and *Smad7$^{fl/fl}$* mice; co-culture experiments of these two cell types were performed to investigate interactions *in vitro*.





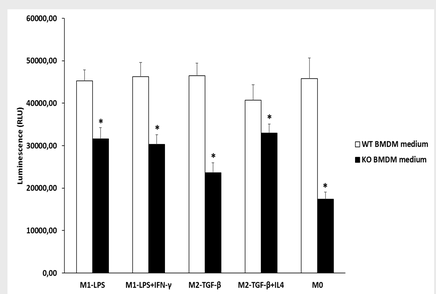
KO unpolarized BMDM exerted a mixed M1/M2 phenotype, and KO M1-polarised BMDM showed a reduced M1 profile compared to control BMDM.

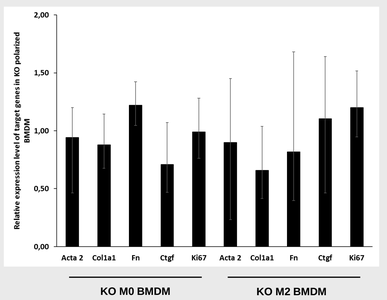


KO mice hade significantly reduced the number of macrophages and fibroblasts.

The latter coinciding with reduced fibronectin expression in experimental CP.

However, this reduction did not result in a decrease of the collagen-based fibrotic index.





Co-culture experiments showed KO BMDM were able to activate PSCs equally well, but were less efficient in supporting PSCs survival.

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