



## Commentary

# From good to bad fibroblasts: New promising targets to cure Chron's disease

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In this study, [1] Ou and colleagues elucidate the mechanism regulating fibroblast activation in Chron's Disease (CD) via YAP/TAZ. Blocking of YAP/TAZ-related mechanisms reduced fibroblast activation in a mouse model of Chron's Disease. The study by Ou et al. identifies YAP/TAZ inhibitors as potential therapeutic targets to treat CD by reducing fibroblast activation.

CD is a chronic inflammatory intestinal disease frequently accompanied by aberrant healing and structuring complications. CD is a life-long, incurable, disabling inflammatory disorder often diagnosed at a young age and continues to increase in frequency worldwide. As of today, therapeutic interventions for this disease are at best limited. Although many therapeutic strategies have been beneficial to block inflammation in CD, no improvement has been made in providing therapeutic strategies to reduce fibrosis. Increasing evidence suggests that the long-lasting inflammation associated with CD is a consequence of activated fibroblasts [2]. However, the mechanisms responsible for fibroblast activation appeared to be independent of those related to immune cell activation [3,4]. Therefore, understanding those mechanisms can potentially open valuable therapeutic strategies to treat CD.

One of the main findings in the study recently published in *EBioMedicine* by Ou et al., is the identification of YAP and YAZ as a mechanism responsible for fibroblast activation. YAP and YAZ proteins are transcription co-activators that respond to multiple inputs regulating the expression of a plethora of genes [5]. YAP aggravates inflammatory bowel disease by regulating macrophage polarization and gut microbiome, [6] and patients with CD present increased YAP/TAZ activation [7]. In line with these reports, the authors showed that the increased expression of YAP and TAZ is associated with CD. However, the paper's novelty is that the authors identified the source of YAP and TAZ upregulation in activated fibroblasts.

Recent data show the beneficial effect of inhibiting YAP and TAZ in the lung in mouse models of lung [8] and liver fibrosis, suggesting this as an effective strategy for treating fibrosis. In addition, the authors study the effect of the in-vivo manipulation of YAP and TAZ using ROCK 1 inhibitor in a mouse model of dextran sulfate sodium induce chronic colitis. ROCK1 inhibition prevents fibrosis in mice developing idiopathic pulmonary fibrosis [9]. Ou et al., showed that suppression of YAP/TAZ via ROCK1 inhibitor alleviated intestinal fibrosis and reduced the severe phenotype of mice that develop chronic colitis. Thus, the compelling data produced by the authors suggest ROCK inhibition as a viable treatment to prevent intestinal fibrosis by targeting YAP and TAZ. Therefore, selective inhibition of YAP/TAZ may hold a beneficial effect in the cure of CD.

There are still numerous questions related to fibroblasts activation that need to be answered. Multiple reports show a strong correlation between fibroblasts activation and changes to immune cell phenotype in CD. We still do not know the mechanism regulating this type of interaction and if activated fibroblasts are responsible for macrophage activation in CD. Further studies are required to determine the nature and the timeline of this communication in the pathophysiology of CD.

### Declaration of competing interest

The author declares has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Contributor

Commentary written solely by GC

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