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Commentary

The Janus-like Face of IL-4Rα in Macrophages during Liver Fibrosis

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Due to their central role as gatekeepers in healthy and diseased conditions, hepatic macrophages are undoubtedly substantial and fascinating immune cells. Liver macrophages are, however, a heterogeneous cell population with impressive, context dependent plasticity. Based on their ontogeny, they can be subdivided into resident tissue macrophages, named Kupffer cells, and macrophages that originate from circulating monocytes, named monocyte-derived macrophages. Both subtypes have crucial functions in liver homeostasis as well as liver diseases (*e.g.*, metabolic diseases, fibrosis and cancer) (Krenkel and Tacke, 2017). In addition, different activation states of macrophages, originally found in cell culture experiments after cytokine stimulation, led to the paradigm of pro-inflammatory "M1" and anti-inflammatory "M2" polarized macrophages.

It is well known that IL-4 receptor alpha (IL-4Rα) signaling mediates a type 2 immune response, resulting in a M2 phenotype in macrophages (Van Dyken and Locksley, 2013). Although this dualism is far too simple to characterize macrophages *in vivo* (especially in the liver!), where macrophage activation/polarization is constantly shaped by systemic triggers and the local microenvironment, it underlines the widespread functional spectrum of these immune cells (Murray, 2017).

For a long time, it has been assumed that liver fibrosis, a scarring process of liver parenchyma caused by sustained hepatic damage, is a unidirectional process. Recent studies have refuted this paradigm and highlighted that macrophages are key players in both directions, fibrosis progression and reversal (Krenkel and Tacke, 2017). In a pioneering study, the depletion of macrophages had opposing effects during progression or regression of hepatic fibrosis in the model of carbon tetrachloride (CCl_4)-induced fibrosis in mice (Duffield et al., 2005). Subsequently, the infiltration of monocyte-derived, Ly6C^{hi} macrophages was found responsible to drive fibrosis progression in this model (Karlmark et al., 2009), but the same cells were capable of switching their phenotype towards restorative, Ly6C^{-} macrophages, which create a fibrolytic microenvironment by modulating the expression of various metalloproteinases (MMPs) (Ramachandran et al., 2012). The molecular mechanisms underlying this macrophage switch and the potential therapeutic implications have yet remained obscure.

In their recent work in *EBioMedicine*, Weng and colleagues discovered opposing (or Janus faced) functions of the IL-4Rα in the CCl_4 mediated murine fibrosis model: In context of fibrosis progression IL-4Rα has a pro-inflammatory and pro-fibrogenic role, whereas an anti-inflammatory and fibrolytic role in fibrosis regression was observed (Weng et al., 2018). During fibrosis progression, IL-4Rα$^{-/-}$ mice showed decreased engraftment of pro-inflammatory Ly6C^{hi} monocyte-derived macrophages into liver, which was associated with attenuated hepatic scarring. This observation was reproduced in the CCl_4 model with LysM-Cre based specific receptor IL-4Rα deletion in myeloid cells (*Il4ra*$^{\Delta LysM}$), from which the authors concluded that IL-4Rα is also relevant for the polarization of tissue-resident macrophages. More convincingly, the pro-fibrogenic role of IL-4Rα was confirmed in experiments, where wild-type mice received antisense oligonucleotides (ASOs) to the *Il4ra* gene during fibrosis progression. The pharmacologic inhibition of IL-4Rα also resulted in impaired collagen deposition in liver, thereby emphasizing ASO based strategies as a potential therapeutic approach in liver fibrosis. Moreover, this intervention influenced the total number of CD68^{+} macrophages in liver, whereas it remains elusive whether resident macrophages (Kupffer cells) or monocyte-derived infiltrating macrophages are the prime target for ASOs in this specific context.

To study the contributions of IL4-Rα to fibrosis regression, mice were treated with ASOs for a period of one week after termination of CCl_4-mediated fibrosis induction. This treatment, as well as fibrosis regression in *Il4ra*$^{\Delta LysM}$ mice, led to an impaired collagen reduction compared to controls. M2 macrophages related genes were suppressed, indicating a change in macrophage activation/polarization, and decreased matrix degradation was related to a reduction of MMP transcripts in *Il4ra*$^{\Delta LysM}$ livers. Additional *in vitro* experiments linked a M2 macrophage phenotype with upregulated MMP-12 expression. However, it is evident that "restorative macrophages" in fibrosis regression have a more complex phenotype than just "M2 macrophages" (Ramachandran et al., 2012).

These results point towards a major challenge in developing novel anti-fibrotic therapies, as the same target (*e.g.*, IL-4Rα) may convey opposing effects during fibrosis progression or regression. Furthermore, it remains to be investigated, if these mechanisms may have additional implications for hepatocarcinogenesis. Most importantly, there are other obstacles that limit the translatability of the current work towards novel pharmacological interventions. The most pressing burden of liver

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diseases in Western countries nowadays relates to non-alcoholic steatohepatitis (NASH) that can progress to liver fibrosis, cirrhosis and cancer (Younossi et al., 2016). Unfortunately, the current work did not confirm a contribution of the IL-4Rα signaling in the fibrogenesis using the methionine-choline deficient (MCD) dietary NASH model in mice. The regulation of IL-4R on human hepatic macrophages, especially in the context of NASH and fibrosis, is also unclear at present.

In this regards, the core value of the current work by Weng et al. is to emphasize the enormous plasticity and diversity of hepatic macrophages with partly opposing (Janus face-like) and context dependent functions (Ritz et al., 2017). While the potential of macrophages as targets for novel therapeutic interventions for liver diseases is obvious from their essential contribution to hepatic fibrosis (Tacke, 2017), the study by Weng et al. reminds us that potential attractive targets such as IL4-Rα need to be thoroughly assessed in disease stage specific conditions to apprehend the complexity of macrophage functions in hepatic fibrogenesis and fibrolysis.

Conflict of Interest

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