Macrophages

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Macrophages: Central regulators of hepatic fibrogenesis and fibrosis resolution

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Summary

Hepatic fibrosis is the common end point to chronic injury of varied aetiology. There is now excellent evidence in both human studies and animal models that liver fibrosis is a bidirectional process with a significant reversible component. The hepatic stellate cell (HSC), following activation to a myofibroblast phenotype, is the principal cell producing extracellular matrix (ECM) during fibrogenesis and is the main source of TIMP-1, which inhibits the endogenous matrix-degrading activity of matrix metalloproteinases (MMPs), thus promoting scar deposition. Furthermore, apoptosis of activated HSCs is a critical feature of scar resolution. However, emerging evidence indicates that it is the hepatic macrophage that is the master regulator of this dynamic fibrogenesis–fibrosis resolution paradigm.

Macrophages can promote fibrogenesis

The key role of macrophages in promoting hepatic fibrogenesis has been demonstrated in a number of studies. Transgenic animals, deficient in the principal macrophage chemokine CCL2-CCR2 axis [1], show reduced monocyte/macrophage infiltration following chronic hepatic injury and are protected from fibrogenesis. Furthermore, utilising a CD11b-DTR system in mice, selective depletion of macrophages during ongoing injury causes a reduction in fibrosis [2]. Additional work has identified a specific Gr-1^{high} subset of hepatic macrophages, derived from recruitment of inflammatory monocytes in a CCR2-dependent manner, as being the principal pro-fibrotic population [3].

So how do macrophages mediate this effect? Closer analysis of fibrotic tissue in human disease and animal models identifies macrophages closely associated with the hepatic scar, directly apposed to the activated HSCs. Macrophages are a rich source of soluble mediators which can act on the HSCs to induce a pro-fibrotic phenotype. Specifically, macrophages can produce and activate the archetypal pro-fibrotic cytokine TGF-β, which acts to increase myofibroblast ECM and TIMP-1 production [3]. Additionally, hepatic macrophages can produce PDGF (a potent stimulator of myofibroblast proliferation), IL-1β and TNF-α (pro-inflammatory cytokines) and a number of chemokines which can induce further inflammatory cell recruitment to perpetuate the pro-inflammatory pro-fibrotic stimulus [4] (Fig. 1).

Macrophages are critical for fibrosis resolution

Emerging evidence now clearly demonstrates that macrophages also have a pivotal role in fibrosis resolution. Selective depletion of hepatic macrophages during the spontaneous recovery phase after chronic CCl_4-induced fibrosis caused a clear failure of hepatic scar remodelling [2]. Additionally, in *CCR2* knockout mice, despite a lower baseline fibrotic response, there is diminished fibrosis resolution following the cessation of injury [1]. Finally, the administration of exogenous macrophages during ongoing hepatic injury can have a significant anti-fibrotic effect [5].

The mechanisms governing the role of the macrophage in fibrosis resolution are still not fully defined and are likely to be multi-factorial, given the immense plasticity in macrophage phenotypes. We have previously shown that macrophages are a rich source of scar degrading MMPs, particularly MMP-13, during the resolution phase *in vivo* [6]. Macrophages are also capable of producing a number of factors, such as MMP-9 or TRAIL, which can promote HSC apoptosis, although a functional role for this mechanism remains to be proven. Additionally, loss of the pro-inflammatory pro-fibrotic signals expressed by macrophages during fibrogenesis might alter the local milieu to favour fibrosis resolution. Indeed, in elegant work by the Tacke group, they defined that CX3CL1 produced by hepatocytes and HSCs in the inflamed liver could signal to infiltrating monocyte-derived macrophages via the CX3CR1 receptor, inducing macrophage survival and an anti-inflammatory phenotype to limit the degree of hepatic inflammation and fibrosis [7]. Macrophages in inflamed tissue also perform the phagocytosis of cellular debris, which removes potential pro-inflammatory signals and may in turn alter macrophage phenotype causing increased MMP expression and enhanced matrix degradation [8]. Furthermore, in renal fibrosis studies serum amyloid P (SAP) protein, a circulating serum protein, binds to apoptotic cells, opsonising them and then signalling via Fcγ receptors on monocytes and macrophages, inducing an

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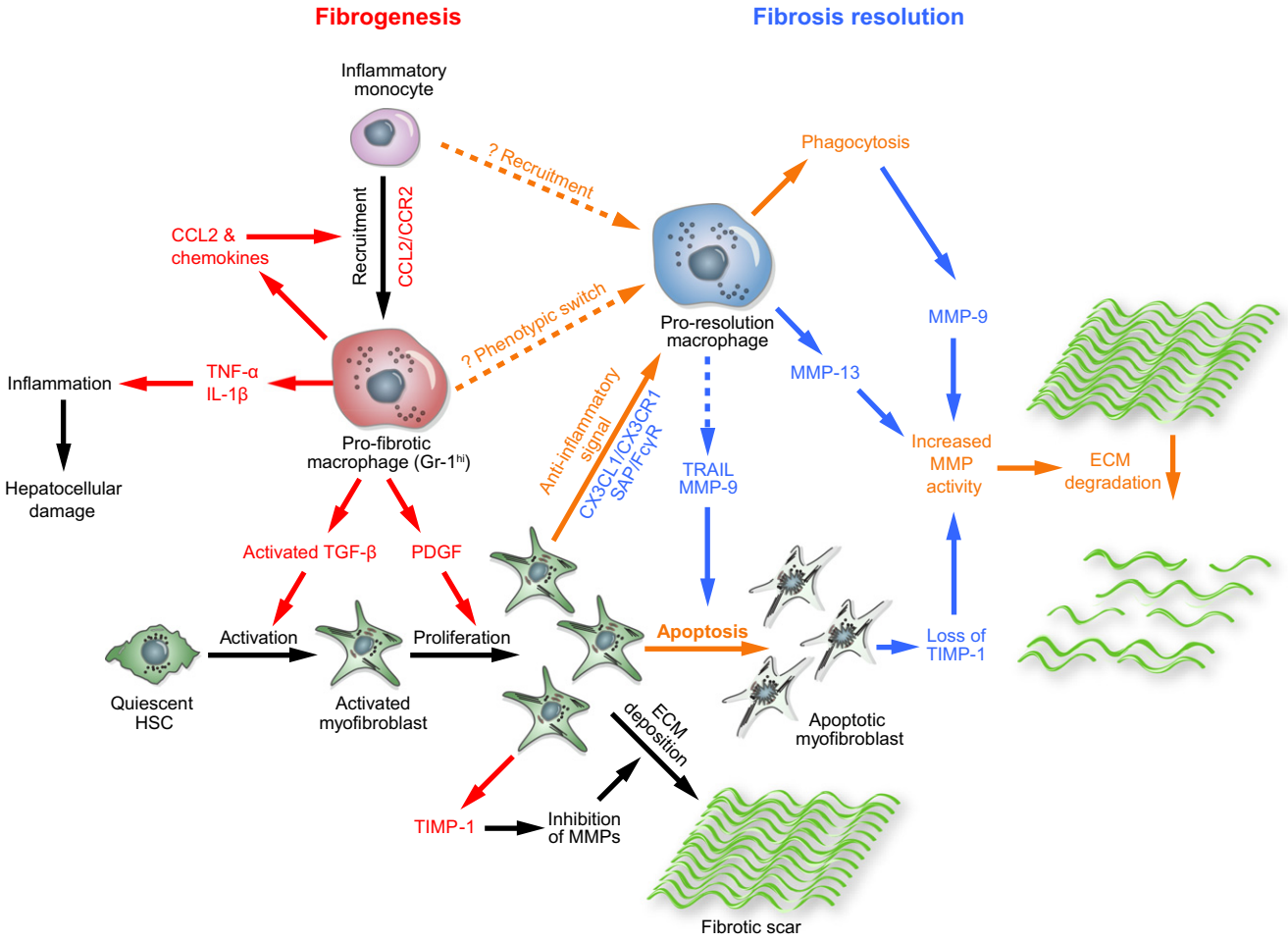

Fig. 1. Macrophages: Central regulators of hepatic fibrogenesis and fibrosis resolution.

anti-inflammatory phenotype with increased IL-10 production and consequent protection from fibrosis [9] (Fig. 1).

The identity of the pro-resolution macrophage

Clearly, macrophages can show significant functional differences in their effects on hepatic fibrosis. It is well described that macrophage populations are heterogeneous in the fibrotic liver, with distinct contributions from resident Kupffer cells and recruited monocytes [2]. Indeed, significant macrophage heterogeneity has been identified by flow cytometry analysis of freshly-isolated human liver, with a $CD14^+$ $CD16^+$ population accumulating in the fibrotic liver and correlating with worsening fibrosis [10]. However, what remains elusive is the identity of the macrophage subset mediating fibrosis resolution. Specifically, do pro-resolution macrophages derive from resident or recruited cells? Does local macrophage proliferation contribute to the formation of distinct populations? Are they formed from pro-fibrotic macrophages by a phenotypic switch *in situ*? What factors induce this switch? What genes do they express to mediate their effect? Answers to these questions in animal models will also permit identification and characterisation of pro-resolution macrophages *in situ* in the human cirrhotic liver. Furthermore, a greater understanding will enable the development of novel therapeutic strategies to manipulate macrophage phenotype *in vivo* and accelerate fibrosis resolution.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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