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LY-6C INTERMEDIATE AND LY-6C^{LO} INTRAHEPATIC MACROPHAGE SUBSETS ORCHESTRATE RESOLUTION OF HEPATIC FIBROSIS FOLLOWING CHRONIC INJURY

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Introduction Hepatic fibrosis is potentially reversible. Macrophages are heterogenous and have distinct roles in fibrogenesis and resolution. Studies have identified a pro-inflammatory Ly-6C^{hi} macrophage subset in mediating fibrogenesis. However, little is known about the identity or phenotype of the restorative hepatic macrophage. Here we identify and characterise the macrophage subset mediating resolution of liver fibrosis following chronic injury.

Methods Liver fibrosis was induced in adult male mice by twice-weekly CCl_4 injections for 4 weeks, followed by histological assessment or flow cytometry analysis at serial time points following cessation.

Results Following cessation of CCl_4 distinct phases of injury and recovery could be identified: active inflammation and fibrogenesis (24 h), peak fibrosis (48–72 h), early resolution with dynamic loss of myofibroblasts and remodelling of majority of scar tissue (72–96 h) and late resolution with degradation of remainder of fibrosis (96–256 h).

Intrahepatic macrophage subsets demonstrated an increase in Ly-6C^{hi} cells during inflammation and fibrogenesis. During resolution there is a rapid loss of these Ly-6C^{hi} cells and emergence of Ly-6C intermediate and Ly-6C^{lo} macrophage subsets. Using CD11B-DTR transgenic mice we depleted macrophages during early resolution, resulting in a failure to remodel hepatic scar. Critically, depletion was selective for the Ly-6C^{int} and Ly-6C^{lo} liver macrophage subsets, and the degree of depletion of these cells correlated significantly with the amount of persistent fibrosis, thus confirming their role in scar resolution. Adoptive transfer and tracking experiments demonstrated that during early resolution the Ly-6C^{int} cells derive from Ly-6C^{hi} circulating monocytes, indicating a phenotypic switch from pro-inflammatory to early pro-resolution macrophages. During late resolution Ly-6C^{lo} monocytes are recruited to replenish resident 'Kupffer' cells.

Gene expression analysis on FACS sorted pro-resolution Ly-6C^{int} macrophages compared with pro-fibrotic Ly-6C^{hi} macrophages demonstrated reduced expression of pro-inflammatory mediators such as IL-1α, IL-1β, IL-6, CXCL2 and MCP-1 and an increase in expression of matrix degrading enzymes such as MMP-12 and MMP-9.

Conclusion We have identified novel Ly-6C^{int} and Ly-6C^{lo} intrahepatic macrophage subsets as central orchestrators in the resolution of liver fibrosis. Critically, during early resolution the Ly-6C^{int} cells derive from a phenotypic switch in pro-fibrotic Ly-6C^{hi} cells, resulting in a change in macrophage gene expression from one promoting fibrogenesis to one favouring fibrosis resolution.

Competing interests None.

Keywords liver fibrosis, Macrophage.