Understanding hepatic macrophage heterogeneity in acute liver injury

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In recent years it has become clear that there are multiple populations of myeloid cells in the inflamed liver including multiple subsets of macrophages (MFs). However, in order to study the specific functions of each subset, we must first be able to identify and distinguish between them.
To study the different populations present in the liver during injury and repair, we have performed single cell RNA sequencing using the 10X genomics platform combined with 20-colour flow cytometry to identify the distinct myeloid cell subsets present at various timepoints post paracetamol overdose. This analysis revealed the presence of 2 subpopulations of MFs based on Clec4F expression. Clec4F+ Kupffer cell (KC) numbers remained largely stable across the timecourse (0-168hrs), while Clec4F- MFs started to accumulate in the liver from 36hrs and had disappeared again by 96hrs. Using shielded BM chimeras, we found that the 2 MF populations have distinct origins with no monocytes contributing to the KC pool, unlike in other inflammatory models or after depletion. Despite changes in the transcriptomes of the recruited monocytes, adoptive transfer studies demonstrated that the lack of moKCs was not due to an intrinsic difference in their ability to generate KCs but rather likely due to differences in their localization, as suggested by confocal microscopy and intravital imaging.
Having identified the distinct subsets of MFs in acute liver injury, we are currently investigating their specific functions. Intriguingly, to date comparison of the KCs and monocyte-derived MFs has not revealed a pro-repair phenotype in the monocyte-derived MFs as suggested. Rather further analysis identified that the Relma+F4/80+CD11bhi cells previously identified as moMFs in the liver 72hrs after paracetamol overdose are a subset of Eosinophils, which upregulate their F4/80 expression, highlighting the need for cell-type specific markers to distinguish between myeloid cells. Thus we are currently also investigating the role of these eosinophils in the wound healing process following acute liver injury.

Keywords : macrophages, acute liver injury, Kupffer cells, paracetamol overdose, single cell
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