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Reply to: "Lack of Kupffer cell depletion in diethylnitrosamine-induced hepatic inflammation"

To the Editor:

"Stay here or disappear": Kupffer cell behaviour during liver injury

Kupffer cells (KC) are liver-resident macrophages that during homeostasis display an overall anti-inflammatory phenotype.[1] Upon infection, KCs critically shape the local inflammatory immune milieu, either by supporting inflammation and controlling the infection, or by maintaining tolerance.[2] Liver injury mostly results from infection or intoxication and is typically accompanied by local inflammatory reactions of varying quality and quantity. Recent studies demonstrated fulminant KC loss during viral or bacterial infection, as well as after toxic hepatic injury.[3–6] Furthermore, upon diphtheria toxin-induced KC depletion infiltrating monocytes can differentiate to monocyte-derived KCs (MoKCs).[7] Similarly, KCs that were depleted during virus-induced hepatitis and then replenished by F4/80$^+$-CLEC4F$^+$ MoKCs were indistinguishable from embryo-derived KCs, when analysed by cell surface receptor expression.[3] Alazawi and Knolle speculated that transient KC loss could be generally associated with liver injury.[8] This hypothesis was followed up by Kessler *et al.* who demonstrated stable KC presence in the model of diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC), even during the acute phase of hepatic inflammation. The authors conclude that different causes of liver inflammation may lead to distinct immune reactions, which do not always result in KC loss. Furthermore, different liver injuries might induce specific alterations in the composition of hepatic myeloid cell subsets as demonstrated in the letter by Kessler *et al.*

Indeed, the DEN model studied by Kessler *et al.* is very different when compared with infection models. This is highlighted by the fact that pathogens not only actively induce, but also modulate immune responses. Therefore, characteristics of the pathogens that induce hepatitis presumably influence the onset and course of liver inflammation and subsequent KC immunity. In particular, direct infection of KCs, as well as inflammation-induced apoptosis, bystander necrosis, or necroptosis may induce KC loss.[4] For several infection-induced cytokines even opposing functions have been identified within the liver, *e.g.* type I interferon might act either in a pro- or anti-inflammatory manner by regulating the composition of other cytokines and chemokines. This way myeloid cell function, including KC disappearance, might be directly and indirectly influenced by different cytokines.[3,9–13]

The liver is a complex and highly structured organ. Therefore, the anatomical site of inflammation might influence KC immunity. KCs are mainly localised in periportal regions. Acute viral hepatitis is often associated with disseminated inflammation throughout the liver. In contrast, toxic inflammation mostly occurs around the portal veins, whereas carcinoma-associated inflammation should primarily occur locally at sites of tumour development. Interestingly, Kessler *et al.* did not detect KC depletion in the DEN model at tumour proximal sites.

Future research should focus on the detailed characterisation of KC development. As outlined above, infiltrating monocytes can replenish KCs by differentiating to CLEC4F$^+$ MoKCs. However, they can also differentiate to short-lived inflammatory macrophages, depending on the kind and extent of liver damage. The functional differences of myeloid cell subsets, their impact on the induction and resolution of liver inflammation as well as their role in liver repair will be of key relevance in order to be able to predict disease course.

Additionally, it is not clear why upon similar liver injuries individuals may show very divergent disease outcomes ranging from entire liver recovery to liver cirrhosis and HCC. Recent studies indicated that individual host characteristics might account for variations in cytokine responses against certain stimuli and infections.[11,12] Thus, in individuals it is possible that selected pathogens induce variable inflammatory responses that are associated with hepatitis and KC depletion, or not. Therefore, it remains necessary to better understand the molec-

ular basis of inflammatory processes that influence myeloid cell subset composition and function during different liver pathologies. Such knowledge will form the basis for the development of new interventions against hepatitis.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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