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Interaction of endothelial cells and innate lymphoid cells in hepatic inflammation and cancer

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The liver is enriched in innate lymphocytes, mainly comprising circulating Natural Killer (NK) cells and liver-resident type 1 innate lymphoid cells (ILC1s), which continuously interact with Liver Sinusoidal Endothelial Cells (LSECs). LSECs line the liver sinusoids and have high endocytic capacities, clearing endo- and exogenous macromolecules from the blood. Innate lymphocytes provide the early defense against infections and malignancies by exerting cytotoxicity and by secreting pro-inflammatory cytokines. However, the local tissue microenvironment that supports NK cell and ILC1 functions in the liver remains not fully explored.

Here, we show that LSECs exposed to inflammatory or tumor cell-derived stimuli, displayed changes in their phenotype and cytokine/chemokine expression profile. Co-culture of NK cells and ILC1s with healthy purified LSECs altered their phenotype and reduced their cytotoxicity against the coloncarcinoma cell line MC38. In contrast, NK cell cytotoxicity was not reduced after encountering tumor cell supernatant pre-exposed LSECs. Thus, LSECs are able to regulate NK cell and ILC1 cytotoxic function against target cells in dependency of received exogenous signals.

During inflammation, LSECs supported NK cell migration via the production of immune cell-attracting chemokines. In livers of LPS-injected mice, accumulating NK cells were the major source of IFN-γ,whereas activated LSECs produced CXCL10. IFN-γ promoted the production of CXCL10 by LSECs, and NK cells migrated towards LSECs in a CXCR3-dependent manner. We show that conditional Cxcl10 gene-deletion in endothelial cells curtailed NK cell accumulation in the liver after LPS treatment in vivo.

In conclusion, our findings unveil that LSECs responded to microbial antigens, immune-derived inflammatory signals, and tumor cell-secreted factors, leading to LSEC activation and chemokine production. We identified LSECs as an important player in NK cell recruitment and anti-tumor functions. Acting as central regulators, LSECs fuel a positive feedback loop of NK cell attraction and activation within the inflamed liver tissue.