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**Novel crosstalk between eosinophils and macrophages controls liver regeneration after ischaemia and reperfusion injury**

Yang Y, Xu L, Atkins C, et al. [Novel IL-4/HB-EGF-dependent crosstalk between eosinophils and macrophages controls liver regeneration after ischaemia and reperfusion injury.](https://gut.bmj.com/content/73/9/1543) Gut 2024; 73:1543-1553. doi: 10.1136/gutjnl-2024-332033.

Ischaemia reperfusion (IR) injury occurring to donor livers during transplantation significantly affects outcomes and requires better understanding. Yang et al., had previously shown eosinophils to be recruited to the liver during IR injury in mouse models. They sought to further characterise this process.

Flow cytometry and immunohistochemical staining showed that after IR injury, eosinophils persist in the liver for up to 5 days, peaking on day 3 which correlates with hepatocyte proliferation. Eosinophil-deficient mice have larger areas of necrosis which resolve on adoptive transfer of eosinophils. This phenomenon prevailed in mouse models of acute liver injury induced by paracetamol and carbon tetrachloride.

Protein analysis revealed IL-4 (interleukin-4) and IL-13 (interleukin-13) to be the most significantly upregulated cytokines after adoptive transfer of eosinophils in eosinophil-deficient mice. Neutralising antibodies against IL-4, but not IL-13, impaired liver regeneration. Flow cytometry identified hepatic macrophages as the main cell type expressing IL-4Rα (interleukin-4 receptor), suggesting the effect of eosinophils is through IL-4/IL-4Rα signalling in macrophages. Indeed, there is impaired hepatic recovery in macrophage-specific IL-4Rα-knockout mice.

These knockout mice express lower levels of phosphorylated-EGFR (epidermal growth factor receptor) compared to wild-type mice, as well as lower levels of a known EGFR ligand, hb-egf (heparin-binding epidermal growth factor-like growth factor). By selectively depleting and replacing hb-egf, Yang et al., showed its expression was essential for promoting hepatic recovery after IR injury.

Thus, eosinophils promote hepatic injury by secreting IL-4, which stimulates hepatic macrophages to produce hb-egf through IL-4Rα. This may offer therapeutic targets to improve or accelerate hepatic recovery after IR injury, improving transplant outcomes as well as potentially expanding the pool of donor organs.