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EP3 signaling in dendritic cells promotes liver repair after ischemia reperfusion injury in mice.

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Macrophage plasticity is essential for liver wound healing; however, the mechanisms of macrophage phenotype switch are largely unknown. Dendritic cells (DCs) are critical initiators of innate immune responses and orchestrate inflammation following hepatic injury. We have shown that PGE_2/EP3 promotes liver repair after hepatic ischemia-reperfusion (I/R). The present study examined whether signaling via EP3 in DCs regulates macrophage plasticity during liver repair by subjecting EP3-deficient ($EP3^{-/-}$) and wild-type (WT) mice to hepatic I/R. Compared with WT mice, $EP3^{-/-}$ mice showed delayed liver repair as indicated by increased levels of ALT and hepatic necrosis, which accompanied by reduced expression of hepatic growth factors. Flow cytometry analysis revealed that accumulation of $Ly6C^{low}$ reparative macrophages and monocyte-derived DCs (moDCs) was suppressed in $EP3^{-/-}$ livers. Adoptive transfer of moDCs from $EP3^{-/-}$ mice resulted in impaired repair, along with increased $Ly6C^{high}$ inflammatory macrophages. When bone marrow macrophages (BMMs) co-cultured with moDCs, BMMs from WT mice, but not from $EP3^{-/-}$ mice up-regulated expression of genes related to a reparative macrophage phenotype. In the presence of an EP3 agonist, interleukin (IL)-13 derived from moDCs drove BMMs to increase expression of genes characteristic of a reparative macrophage phenotype. The results suggest that EP3 signaling in moDCs facilitates liver repair by inducing IL-13-mediated switching of macrophage phenotype from pro-inflammatory to pro-reparative.