Essential involvement of a chemokine receptor, CCR2, to liver metastasis

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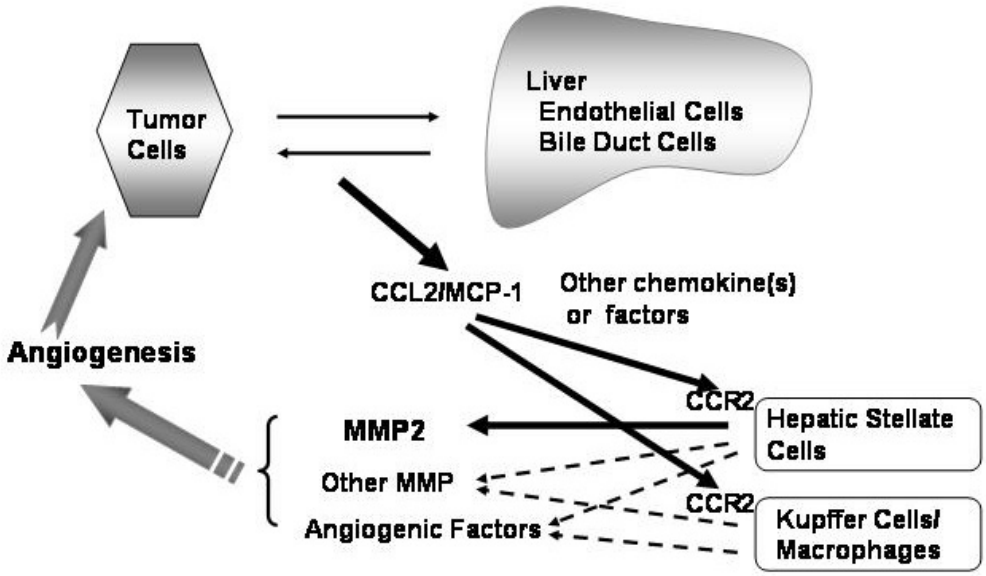
The liver parenchyma is populated by hepatocytes and several non-parenchymal cell types including Kupffer cells (KC) and hepatic stellate cells (HSC). Both KC and HSC are responsive to the chemokine CCL2, but the precise roles of CCL2 and these cells in liver tumor formation remain undefined. Hence, we investigated the effects of the lack of the major CCL2 receptor, CCR2, on liver tumor formation induced by intraportal injection of the murine colon adenocarcinoma cell line, colon 26. Wild-type mice showed macroscopic tumor foci in the liver 10 days after injection of colon 26 cells. After 10 days, CCL2 proteins were detected predominantly in tumor cells, coincident with increased intratumoral KC and HSC numbers. Although tumor formation occurred at similar rates in wild-type and CCR2-deficient mice up to 10 days after tumor cell injection, the number and size of tumor foci were significantly attenuated in CCR2-deficient mice relative to wild-type mice thereafter. Moreover, neovascularization and matrix metalloproteinase (MMP) 2 expression were diminished in CCR2-deficient mice with a concomitant reduction in the accumulation of KC and HSC. MMP2 was detected predominantly in HSC but not in KC. Thus, CCR2-mediated signals can regulate the trafficking of HSC, a main source of MMP2, and consequently can promote neovascularization during liver tumor formation.



Reference
Yang X, et al. Intl. J. Cancer 118: 335, 2006.