Essential contribution of a chemokine, CCL3, and its receptor, CCR1, to hepatocarcinogenesis

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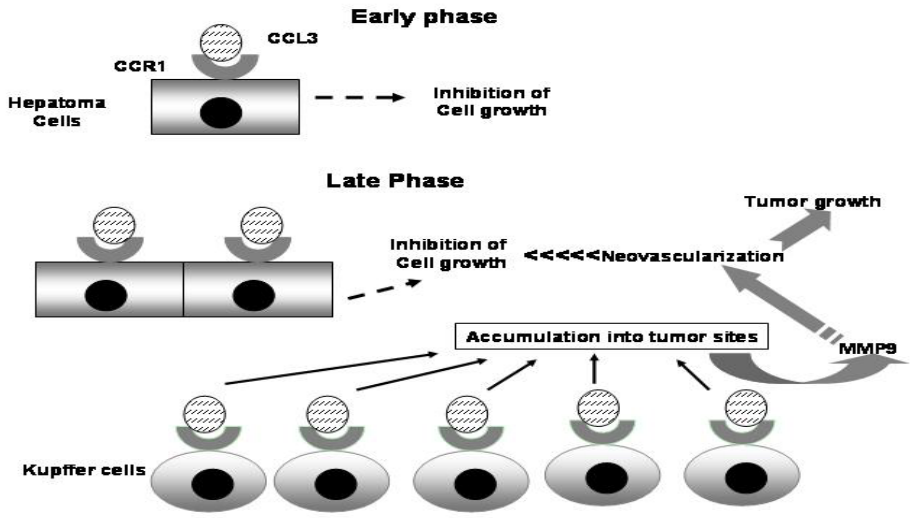
We previously observed that a chemokine, macrophage inflammatory protein-1 α/CCL3, and its receptor, CCR1, were aberrantly expressed in human hepatocellular carcinoma (HCC) tissues (1). We further demonstrated that CCL3 and CCR1 are also expressed in two different models of this cancer; *N*-nitrosodiethylamine (DEN)-induced HCC and HCC induced by hepatitis B virus surface (HBs) antigen-primed splenocyte transfer to myelo-ablated syngeneic HBs antigen transgenic mice (2). At 10 months after DEN treatment, tumor incidence was marginally but significantly higher in CCR1- and CCL3-deficient mice than WT mice, in line with the in vitro observation that CCL3 can inhibit the proliferation of hepatoma cell lines. On the contrary, foci numbers and sizes were remarkably reduced in CCR1- and CCL3-deficient mice, compared with wild-type mice. Of note is that tumor angiogenesis was also markedly diminished in CCL3- and CCR1-deficient mice, with a concomitant reduction in the number of intratumoral Kupffer cells, a rich source of growth factors and matrix metalloproteinases (MMPs). Among growth factors and MMPs that we examined, only MMP9 and MMP13 gene expression was augmented progressively in liver of WT mice after DEN treatment. Moreover, MMP9 but not MMP13 gene expression was attenuated in CCR1- and CCL3-deficient mice, compared with wild-type mice. Furthermore, MMP9 was expressed mainly by mononuclear cells, and MMP9-expressing cell numbers were decreased in CCR1- or CCL3-deficient mice, compared with wild-type mice (2). These observations suggest that the CCR1-CCL3 axis has different roles in HCC progression, depending on its phases (see below Figure).



References

1) Lu P, et al. Am. J. Pathol. 162: 1249, 2003.
2) Yang X, et al., Intl. J. Cancer [Epub ahead of print] PMID: 16284949