Essential contribution of the CCL3-CCR5 axis to murine lung metastasis process

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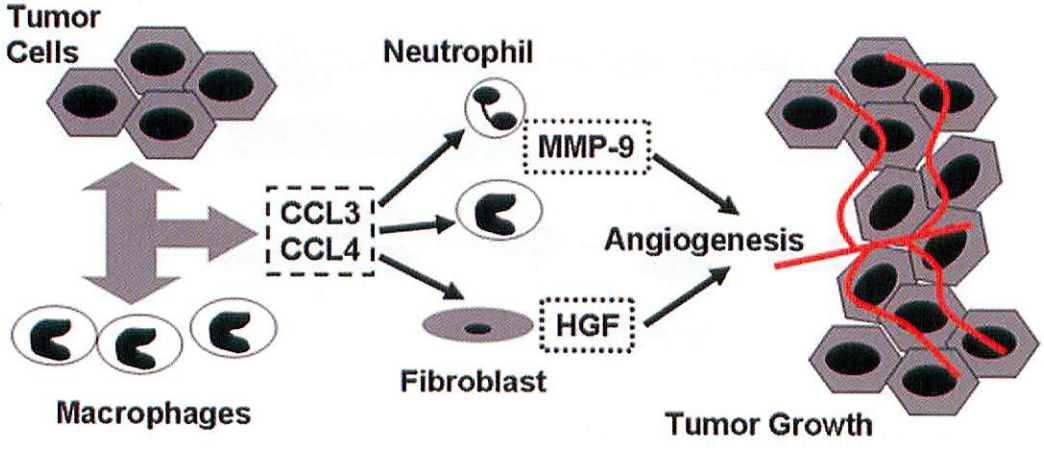
Metastasis proceeds through interaction between cancer cells and resident cells such as leukocytes and fibroblasts. An intravenous injection of a mouse renal cell carcinoma, Renca, into wild-type (WT) mice, resulted in multiple metastasis foci in lungs and was associated with intratumoral accumulation of macrophages, granulocytes, and fibroblasts. A chemokine, CCL3, was detected in infiltrating cells and to a lesser degree, tumor cells, together with an infiltration of leukocytes expressing CCR5, a specific receptor for CCL3. A lack of *CCL3* or *CCR5* gene reduced the number of metastasis foci in the lung. The analysis using bone marrow chimeric mice revealed that both bone marrow- and non-bone marrow-derived cells contributed to metastasis formation. CCL3- and CCR5-deficient mice exhibited a reduction in intratumoral accumulation of macrophages, granulocytes, and fibroblasts. Moreover, intratumroal neovascularization, an indispensable process for metastasis, was attenuated in these gene deficient mice. Intrapulmonary expression of matrix metalloproteinase (MMP)-9 and hepatocyte growth factor (HGF) was enhanced in WT mice and the increases were markedly reduced in CCL3- and CCR5-deficient mice. Furthermore, MMP-9 protein was detected in macrophages and granulocytes, the cells which also express CCR5 and *in vitro* stimulation by CCL3 induced macrophages to express MMP-9. Intratumoral fibroblasts expressed CCR5 and HGF protein. Fibroblasts *in vitro* exhibited chemotactic responses and expressed HGF in response to CCL3. Collectively, the CCL3-CCR5 axis appears to regulate intratumoral trafficking of leukocytes and fibroblasts, and MMP-9 and HGF expression, and as a consequence to accelerate neovascularization and subsequent metastasis formation.



Reference
Wu Y et al. (2008) J. Immunol. 181: 6384-6393.