Targeting CCL2/CCR2 signalling as a therapeutic strategy against hepatocellular carcinoma

With the support by the National Natural Science Foundation of China, Ministry of Science and Technology of China, and Chinese Academy of Sciences, a research team led by Dr. Wang Hui (**王慧**) at the Institute for Nutritional Sciences, SIBS, Chinese Academy of Sciences reported recently that targeting CCL2/CCR2 is a promising therapeutic strategy against hepatocellular carcinoma (HCC), which was published in *Gut* (2015, Oct 9, [Epub ahead of print]).

HCC is an aggressive malignancy with limited effective treatment options. An alternative strategy is to target cells, such as tumor-infiltrating macrophages, in the microenvironment of liver cancers. Tumor-associated macrophages (TAMs) are believed to promote cancer initiation and malignancy and to be involved in tumor development, tumor control, and response to treatment. The CCL2/CCR2 axis is required for recruitment of monocytes/macrophages and is implicated in various aspects of liver pathology, including acute liver injury, chronic hepatitis, cirrhosis, and tumorigenesis.

In two independent cohorts, CCL2 is overexpressed in human HCCs and is associated with a poor prognosis for patients. The CCL2/CCR2 signaling axis mediates cross-talk between tumor cells and stromal cells and supports the growth and metastasis of liver cancer cells. They found that blocking CCL2/CCR2 signaling with a novel CCR2 antagonist inhibits HCC growth and metastasis, reduces post-surgical recurrence, and enhances survival. Mechanistically, CCR2 antagonist inhibits the number of peripheral blood inflammatory monocytes and tumor-infiltrated TAMs, suppresses the M2 polarization of macrophages and overcomes the immunosuppressive effect of TAMs on cytotoxic T lymphocytes. The results from the present study have high potential for translation to clinical practice. The findings not only explore the mechanism of CCL2/CCR2-mediated cross-talk among tumor cells, macrophages, and cytotoxic T lymphocytes in the tumor microenvironment, but also identify tumor-infiltrating macrophages as a therapeutic target for HCCs, and demonstrate the translational potential of CCL2/CCR2 blockade for treatment of HCCs.

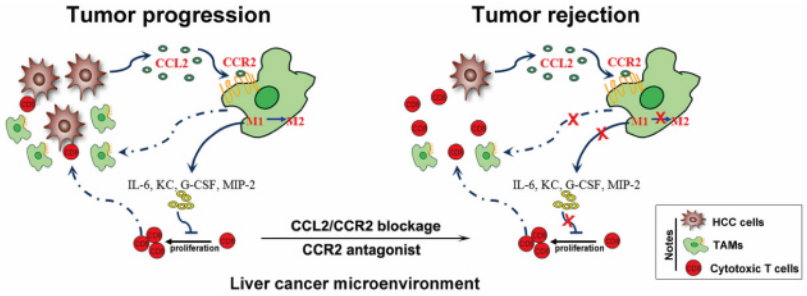

Figure CCR2 antagonist targets tumor-associated macrophages and activates an antitumoral $CD8^+$ T cell response.