Medicine / Healthcare, Tumor immunity

Regulation of endogenous chemokines for activating anti-tumor immunity and its therapeutic potential in intrahepatic cholangiocarcinoma

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Abstract

Intrahepatic cholangiocarcinoma (iCCA) is a refractory neoplasm with a dismal outcome. It has become increasingly important to regulate the interplay between tumor and tumor microenvironment to overcome this malignancy. CXCL9, an IFN-γ inducible chemokine, is involved in tumor immunity by acting as a chemoattractant to direct the migration of activated immune cells. Here, we sought to determine the impact of endogenous CXCL9 on tumor immune microenvironment in iCCA.

Background & Results

Chemokines, released by either tumor cells or surrounding cells, greatly contribute to the recruitment of immune cells to tumor microenvironment. We previously reported that intra-graft CXCL9 was a most sensitive biomarker of acute cellular rejection after liver transplantation. This indicates CXCL9 is a key modulator of liver cellular immunity and would play a central role in the regulation of tumor immunity in iCCA. We, therefore, aimed to clarify the significance of endogenous CXCL9 on tumor immunity in iCCA. First, endogenous CXCL9 expression and the number of tumor-infiltrating lymphocytes were immunohistochemically assessed using resection specimens. High CXCL9 expression in tumor was closely associated with prolonged postoperative survival and a large number of $NCR1^+$ tumor-infiltrating natural killer (NK) cells. Next, we validated this fact in mice treated by silencing CXCL9 with short hairpin (sh) RNA. CXCL9-defficient cells were more tumorigenic in the liver than CXCL9-sufficient cells. Flow cytometry analyses revealed that the trafficking of total, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expressing, and CXCR3 expressing NK cells into tumors was significantly lessened in tumors with CXCL9-defficient cells compared to those with CXCL9-sufficient cells. Lastly, we showed that the depletion of NK cells using the PK136 antibody eliminated the volume differences between CXCL9-deficient and CXCL9-sufficient tumors. Taken together, our findings suggest that endogenous CXCL9 drives tumor-infiltrating NK cells, which in turn determines the growth of iCCA.

Significance of the research and Future perspective

The advent of immune checkpoint inhibitors reaffirms us the importance of tumor immunity. However, only a small subset of patients has gained the survival benefits from these drugs so far and the development of effective drugs that can favorably alter tumor immune microenvironment remains challenging. In the current study, we clarified that endogenous CXCL9 in tumor contributed to the recruitment of NK cells into tumor and affected patient prognosis in iCCA. These results indicate that the regulation of endogenous chemokines may offer a new therapeutic approach in various types of cancer. High-throughput screening of compound libraries in future studies would help us identify new drug candidates which can augment anti–tumor immune surveillance and boost the effects of chemotherapies or immune checkpoint inhibitors via the regulation of endogenous chemokines.

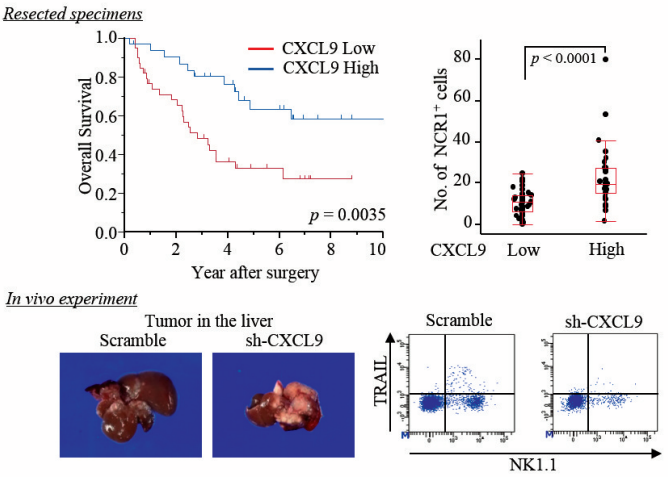

Fig. 1: Significance of endogenous CXCL9 in intrahepatic cholangiocarcinoma

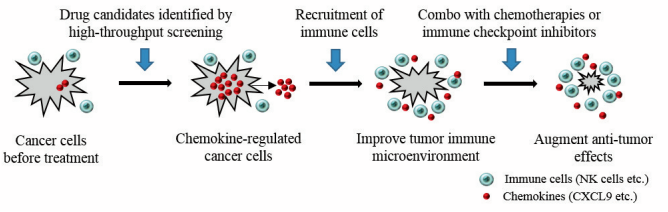

Fig. 2: Boosting the effects of chemotherapies and immune checkpoint inhibitors by the regulation of endogenous chemokines

Patent
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