The mechanisms of MCP-1 production in tumor microenvironments: Tumor cells are not home alone

When you look at tumors, you may think they are composed of 100% tumor cells. The fact is that tumor tissues contain not only tumor cells but also a variety of non-tumor stromal cells, including fibroblasts, endothelial cells and inflammatory cells (Fig. 1). The interaction of tumor cells with stromal cells leads to the production of an array of mediators that provide the soil in which tumor cells grow, invade and metastasize. These mediators include matrix metalloproteinases, growth factors, cytokines and chemokines. Monocyte chemoattractant protein-1 (MCP-1, also known as CCL2) is a 76-amino acid protein belonging to the family of proteins (chemokines) regulating the trafficking of leukocytes. The main activity of MCP-1 is to recruit blood monocytes into sites of inflammation and tumors. Since MCP-1 production in tumors facilitates the accumulation of macrophages (so called tumor associated macrophages, TAMs) which are immuno-suppressive and tumor-promoting, it has become a molecular target for cancer treatment.

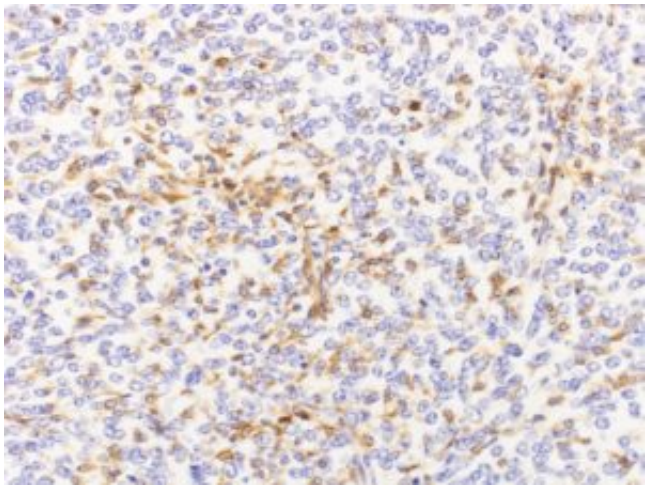

Fig. 1. Infiltration of macrophages into 4T1 tumor. Macrophages were stained positive by immunohistochemistry using an anti-F4/80 antibody. 400X magnification.

A number of tumor cell lines which we use in the laboratory produce MCP-1 without additional stimuli in culture; therefore, tumor cells were originally thought to be the primary source of this protein in established tumors. However, recent studies strongly suggest that stromal cells are the primary cell source of MCP-1 in some tumors. There are three potential mechanisms by which MCP-1 production is increased in tumors; 1) MCP-1 production is constitutively increased by tumor cells, 2) tumor cell production of MCP-1 is increased in response to stimuli, and 3) stromal cell production of MCP-1 is increased by interacting with tumor cells. We recently attempted to determine the mechanisms of MCP-1 production in tumors using two mouse tumor models; 4T1

breast cancer and Lewis lung carcinoma (LLC) model (Fig. 2).

In 4T1 tumors, the main source of MCP-1 is non-tumor stromal cells and stromal cell-derived MCP-1 promotes spontaneous metastasis of 4T1 cells to the lung. 4T1 cells do not produce a high level of MCP-1 even when they are stimulated with potent tumor cell activators, such as the toll-like receptor 4 ligand lipopolysaccharide or the cytokine tumor necrosis factor (TNF). Instead, they produce and release granulocyte-macrophage colony-stimulating factor (GM-CSF, also known as colony-stimulating factor-2) that activates macrophages to produce a high level of MCP-1. This is just one mechanism in this model and other unidentified mechanisms are also involved.

By contrast, activated tumor cells are the main source of MCP-1 in LLC tumors. In this case, tumor cells produce and release an unidentified molecule that activates macrophages to produce and release TNF. As noted above, TNF is a potent tumor cell activator and macrophage-derived TNF induces a high level MCP-1 production by LLC cells. Unlike 4T1 cells, LLC cells have a much larger capacity to produce MCP-1, resulting in a much higher MCP-1 level in this tumor than in 4T1 tumor.

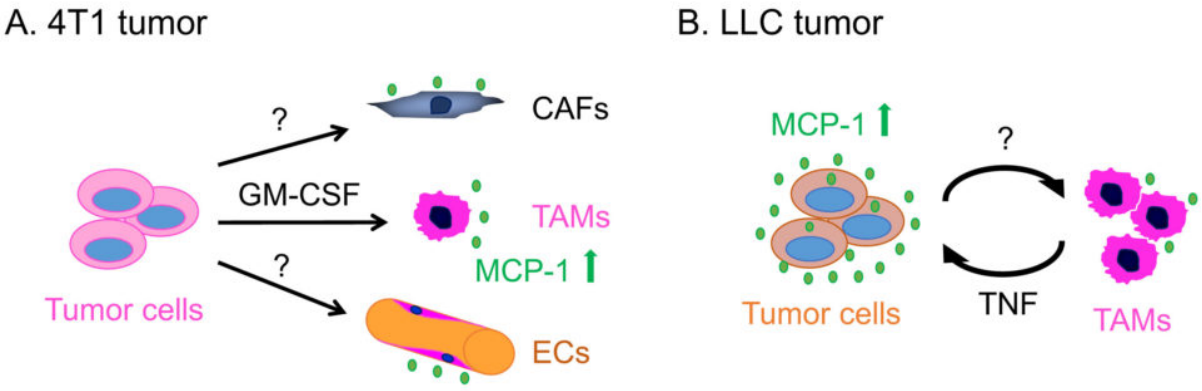

Fig. 2. The mechanisms of MCP-1 production in 4T1 and LLC tumor. A. The capacity of 4T1 cells to produce MCP-1 is low. However, they are able to activate stromal cells to produce a sufficient amount of MCP-1 for lung metastasis. For example, they produce and release GM-CSF, which up-regulates the production of MCP-1 and other cytokines/chemokines by macrophages. Activated CAFs and endothelial cells could be additional sources of MCP-1. CAF, cancer-associated fibroblasts; EC, endothelial cells; TAM, tumor-associated macrophage. B. LLC cells harbor the activating KrasG12C mutation and this mutation causes constitutive MCP-1 production. An unidentified product of LLC cells activates TAMs to produce and release TNF. This TNF activates LLC cells to further up-regulate MCP-1 production. The level of MCP-1 produced by LLC tumors is much higher than that by 4T1 tumors.

By examining the mechanisms of MCP-1 production in tumor microenvironments, we have learned two different ways tumor cells use to communicate with stromal cells for their progression. However, we have not identified all mechanisms involved in tumor cell-stromal cell interaction even in these two models. Tumor cells likely use additional mechanisms in other types of tumors for their benefit. We have also learned that the level of MCP-1 required for 4T1 cells to metastasize to the lung is not very high, raising a possibility that high levels of MCP-1 detected in cancer patients may just reflect the character of tumor cells. Our ultimate goal is to identify the mechanisms by which tumor cells interact with stromal cells to create a tumor-promoting microenvironment and to provide a new means to save lives of patients with cancer.

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