General Summary of Division of Molecular Bioregulation

Tumor cells and resident cells can produce various chemokines and pro-inflammatory cytokines, during carcinogenesis and metastasis processes. The produced chemokines and pro-inflammatory cytokines can modulate the microenvironment of tumor tissues, thereby affecting carcinogenic and/or metastatic processes. A major research object in our division is to elucidate the roles of these endogenously produced chemokines and pro-inflammatory cytokines in these processes, in order to use these molecules and/or their antagonists for the treatment of cancer.

We originally identified a serine/threonine kinase, Pim-3, as a proto-oncogene expressed selectively in chronic inflammation-mediated hepatoma tissues in mice. Our subsequent studies have unraveled that Pim-3 is enhanced selectively in malignant lesions of endoderm-derived organs and can counteract apoptotic cell death of cancer cells. These observations prompt us to investigate the possibility of the development of an anti-cancer drug by targeting Pim-3.

A) Chemokines and pro-inflammatory cytokines in carcinogenesis and metastasis processes

Tumor cells as well as resident normal cells can produce a wide variety of chemokines and pro-inflammatory cytokines, thereby affecting the course of carcinogenesis and metastasis processes. Until present, we have provided definitive evidence to indicate that tumor necrosis factor receptor p55 has crucial roles in inflammation-mediated colon carcinogenesis, liver metastasis, and lung metastasis. Moreover, we demonstrated that tumor cells and resident normal cells can produce various chemokines and that the produced chemokines have effects on tumor cells as well as inflammatory cells, thereby contributing to carcinogenesis and metastasis processes.

B) Pim-3, a proto-oncogene with serine/threonine kinase activity, in carcinogenesis

Pim-3 is aberrantly expressed in malignant cells and lesions of endoderm-derived organs, including liver, pancreas, colon, and stomach. Pim-3 can inactivate a pro-apoptotic molecule, Bad, by phosphorylating its Ser^{112} residue, thereby preventing apoptotic cell death. Thus, Pim-3 may be a good molecular target for treating tumors, which exhibit the enhanced expression of Pim-3. We are now developing a chemical with a low molecular weight, which can inhibit the cell proliferation of cancer cells by inhibiting Pim-3 kinase.