

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Mast Cells and Pancreatic Cancer

Theoharis C. Theoharides, Ph.D., M.D.

Pancreatic ductal adenocarcinoma is probably the most lethal cancer, with a median survival of less than 6 months and a 5-year survival rate of less than 5%. The cause of pancreatic ductal adenocarcinoma is unknown, and this type of cancer resists all currently available treatments. Increasing evidence indicates that inflammation around tumors, including infiltration by mast cells, facilitates cancer growth, especially that of pancreatic ductal adenocarcinoma.¹

Mast cells are derived from a unique bone marrow precursor, and they mature in the tissues. They are commonly known for their role in allergic and anaphylactic reactions, during which they secrete numerous vasoactive, chemoattractant, and inflammatory molecules as well as growth factors.² In addition to allergic triggers, mast cells participate in inflammation; they can be activated by nonallergic triggers (Fig. 1),³ many of which are expressed by the cells of pancreatic ductal adenocarcinoma.

Soucek et al.⁴ report that the activation of the Myc oncogene protein in mice induces rapid development of pancreatic islet tumors that is dependent on the recruitment of mast cells. Myc is a pleiotropic transcription factor that contributes to tumor angiogenesis, growth, proliferation, and stromal remodeling. Soucek and colleagues observed that Myc activation rapidly (within 24 hours) induced the release of mast-cell chemoattractants — in particular, the CC chemokine ligand 2 (CCL2, also known as monocyte chemoattractant protein 1) in the islet-associated stroma. Mast cells were the only inflammatory cells increased in the vicinity of tumor cells at this early time, and their infiltration correlated with the expansion of islet tumors. The presence of mast cells was also required for the maintenance of established tumors in this animal model. Treatment of the mice with the mast-cell stabilizer disodium cromoglycate (cro-

molyn) led to tumor hypoxia and tumor-cell apoptosis. Moreover, tumors could not be induced in mast-cell-deficient mice. Myc activation was not affected in the mast-cell-deficient mice, indicating that the absence of mast cells, rather than aberrant Myc function, prevented the growth of pancreatic tumors. The authors then showed that the absence of tumor expansion in mast-cell-deficient mice was due to a defect in tumor angiogenesis.

In summary, Soucek et al. showed that Myc activation leads to rapid mast-cell recruitment through CCL2, mast cells are required for the angiogenesis and growth of pancreatic tumors, and the inhibition of mast-cell activation is sufficient to result in tumor death. However, they did not identify the tumor-derived mast-cell stimulants, nor did they identify mast-cell-derived molecules that are involved in tumor angiogenesis. Since cromolyn blocks mast-cell degranulation and secretion of most mediators in mice, it is difficult to ascertain which mediators may be involved in the Myc-induced growth of islet tumors. The authors conclude that mast cells are necessary for tumor angiogenesis and vascular maintenance; they further suggest that inhibition of mast-cell function may prove to be therapeutically useful in restraining the growth of pancreatic cancer.

Many mast-cell mediators that could be considered “protumor” (Fig. 1) include heparin, metalloproteinases, platelet-derived growth factor, and vascular endothelial growth factor (VEGF).⁴ However, mast cells also release molecules that could participate in tumor death and be considered “antitumor.” Consequently, Myc activation may lead not only to mast-cell recruitment, but also to selective secretion³ by mast cells of angiogenic mediators such as VEGF.⁵

Unfortunately, even though cromolyn inhibits mast cells in mice, it is a weak inhibitor of hu-

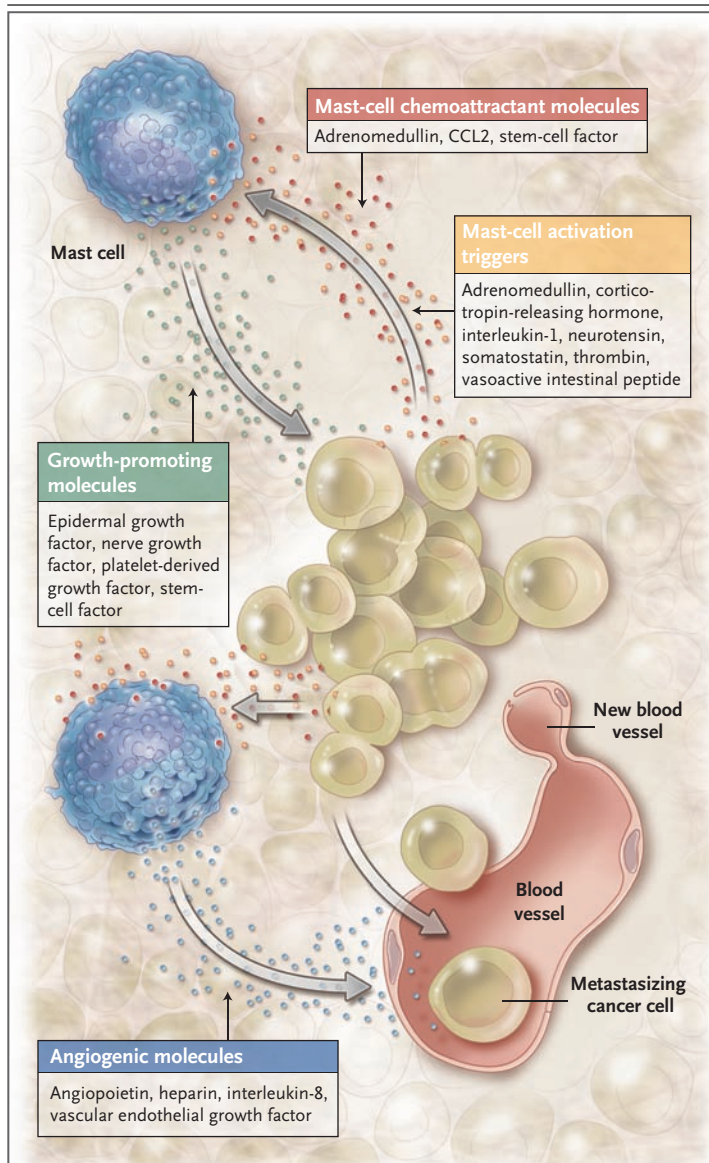


Figure 1. A Model of the Mast Cell in Pancreatic Cancer.

Pancreatic cancer secretes chemoattractants that recruit mast cells to its vicinity. Mast cells are then activated either by direct contact or by cancer-cell–derived triggers to release “procancer” mediators selectively. These mediators induce angiogenesis, promote tumor proliferation, inhibit immune responses, and break down the surrounding stroma to permit metastases. CCL2 denotes chemokine ligand 2.

man mast-cell secretion and is poorly absorbed, so it is unlikely to be effective in treating pancreatic cancer in humans. In fact, there are no effective, clinically available mast-cell blockers. It would be clearly beneficial to have access to mast-cell inhibitors that block the secretion of protumor mediators while permitting the secretion of anti-tumor mediators. In addition, it would be beneficial if such inhibitors would be targeted to mast cells only by being linked to molecules that recognize cell-surface markers unique to the mast cell. Intraperitoneal administration of such inhibitors might be indicated in patients with pancreatic ductal adenocarcinoma to permit therapeutic concentrations and reduce potential adverse effects.

The name “mastzellen” (derived from the Greek word “masto,” which means “to feed”) was chosen by Dr. Paul Ehrlich in his 1887 doctoral thesis. It may turn out that this term was prophetic at least for tumor nourishment: it is now clear that mast cells can promote both neoangiogenesis and tumor growth.

Dr. Theoharides reports holding patents on mast-cell inhibitors to treat atopic allergic diseases and on proteoglycans to treat inflammatory processes resulting from the activation of mast cells in the bladder, prostate, brain, and skin and in arthritis and cardiovascular disease. No other potential conflict of interest relevant to this article was reported.

From the Tufts University School of Medicine and Tufts Medical Center — both in Boston.

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