Mast cells in pancreatic ductal adenocarcinoma

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Using in vivo models of pancreatic ductal adenocarcinoma (PDAC), we demonstrated that mast cells migrate to the tumor site and provide a microenvironment that allows for tumor progression. These results indicate that targeting mast cells may be a promising novel therapy for PDAC.

Mast cells regulate adaptive immune responses via the release of cytokines and other immunomodulatory factors. These factors can promote immune suppression and may contribute to tumor progression progression. The important roles of mast cells have been reported in many human malignancies. However, the role of mast cells in human PDAC remains obscure.

We hypothesized that mast cells in the tumor microenvironment are essential for PDAC tumorigenesis. To test this hypothesis, we employed several in vivo animal models. First, we used a transgenic K-rasG12V spontaneous PDAC mouse model and observed an early influx of mast cells to the tumor microenvironment, which suggests that mast cells in the tumor microenvironment are essential for PDAC tumorigenesis.

We then investigated the contribution of mast cells to PDAC tumorigenesis by using a mast cell-deficient mouse model (Kitw-sh/w-sh). We further assessed the clinical relevance by correlating mast cell infiltration with the survival of patients with PDAC. Our results indicate that mast cells play a key role in the tumor microenvironment and may play a novel therapeutic target.

To measure mast cell influx during the development of PDAC, we utilized a transgenic K-rasG12V mouse model that developed CP, PanINs, and invasive PDAC. Pancreatic tissue was obtained at various stages and grouped by pathologic results: NP (n = 9), CP (n = 9), PanIN (n = 9), and PDAC (n = 4). Pancreatic tissues were obtained from WT littermates served as controls. We determined when and how much mast cells infiltrate the PDAC tumor microenvironment. The influx of mast cells in CP persisted through the development of PanIN and PDAC. There was no significant difference in mast cell scores between CP and different stages (i.e., I-III) of PanIN and PDAC. While mast cells were evenly distributed in CP and PanIN lesions, they accumulated at the infiltrating edges of the tumor. Our results showed that mast cell infiltration was an early event and that mouse mast cells infiltrate the PDAC tumor microenvironment and may play a critical role in PDAC development.

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To further confirm the hypothesis that mast cells promote PDAC tumorigenesis, we employed a mast cell reconstitution mouse model. Bone marrow-derived mast cells from WT C56BL/6 mice were injected into mast cell-deficient Kitw−/− mice and repopulated in the pancreatic tissues. Tumor growth was significantly increased in the Kitw−/− mice repopulated with mast cells compared with the parental Kitw−/− mice (p = 0.009). Mast cell reconstitution also increased the incidence of hemorrhagic ascites to 50%. The repopulation of mast cells was confirmed by both hematoxylin and eosin and toluidine blue staining. These data support the critical role of mast cells in PDAC progression.
To determine the clinical relevance of mast cell influx in PDAC, we stained 67 pancreaticoduodenectomy specimens from a previously constructed tissue microarray with toluidine blue and counted the mast cells (Fig. 1A–E). Patients with mast cell scores $>3.68$ survived significantly longer (median overall survival duration, 36.2 ± 9.4 mo) than did patients with mast cell scores $\leq 3.68$ (median overall survival duration, 13.4 ± 3.4 mo; p = 0.008, high vs. low mast cell infiltration) (Fig. 1F).

In addition, the incidence of recurrence was lower in patients with mast cell scores $>3.68$ (67%) than in patients with mast cell scores $\leq 3.68$ (100%; p = 0.003, Fisher’s exact test.)

In summary, we demonstrated that mast cells play a role in the development and progression of PDAC, a deadly disease with limited treatment options. We found (1) an early influx of mast cells in 

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mutation-driven spontaneous PDAC, which mimics human PDAC, (2) the necessity of mast cells in vivo for PDAC tumor growth and (3) the clinical relevance of mast cells in PDAC. These findings indicate that mast cells are essential for PDAC progression and present a potential therapeutic target.

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Figure 1. Association of mast cell infiltration with survival of patients with PDAC. No mast cells were found in NP tissues. (A) 100x and (D) 400x. (B) A human PDAC tissue microarray was stained with toluidine blue. Mast cells were found in the human PDAC tumor microenvironment: (C) 100x and (E) 400x. Mast cells stained red-purple (metachromatic staining), and the background was blue (orthochromatic staining). (F) The mast cell score was correlated with survival in patients with PDAC. The mast cell score was normalized as the ratio of the number of mast cells to the percentage of pan-leukocytes (CD45-positive cells). The cutoff point of the mast cell score was set at 3.68. Upper curve, patients with mast cell scores $>3.68$; lower curve, patients with mast cell scores $\leq 3.68$. The p value was derived using the log-rank statistic.