Mast Cells in Tumor Microenvironment Promotes the In Vivo Growth of Pancreatic Ductal Adenocarcinoma

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Abstract

Purpose: Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death. No effective therapy is currently available for PDAC because of the lack of understanding of the mechanisms leading to its growth and development. Inflammatory cells, particularly mast cells, have been shown to play key roles in some cancers. We carried out this study to test the hypothesis that mast cells in the tumor microenvironment are essential for PDAC tumorigenesis.

Experimental Design: The presence of inflammatory cells at various stages of PDAC development was determined in a spontaneous mouse model of PDAC (K-rasG12V). The importance of mast cells was determined using orthotopically implanted PDAC cells in mast cell–deficient Kitw-sh/w-sh mice and further confirmed by reconstitution of wild-type bone marrow–derived mast cells. Clinical relevance was assessed by correlating the presence of mast cells with clinical outcome in patients with PDAC.

Results: In the spontaneous mouse model of PDAC (K-rasG12V), there was an early influx of mast cells to the tumor microenvironment. PDAC tumor growth was suppressed in mast cell–deficient Kitw-sh/w-sh mice, but aggressive PDAC growth was restored when PDAC cells were injected into mast cell–deficient mice reconstituted with wild-type bone marrow–derived mast cells. Mast cell infiltration into the tumor microenvironment was predictive of poor prognosis in patients with PDAC.

Conclusions: Mast cells play an important role in PDAC growth and development in mouse models and are indicative of poor prognosis in humans, which makes them a potential novel therapeutic target.

Introduction

Pancreatic ductal adenocarcinoma (PDAC), whose nomenclature derives from its histologic resemblance to ductal cells, is the most common pancreatic malignancy, and an estimated 213,000 new cases are diagnosed worldwide annually (1). It is the fourth leading cause of cancer death in the United States, with very dismal survival rates. Median survival duration after diagnosis is 3 to 6 months, and the 5-year survival rate is less than 5%, which is the lowest survival rate of all cancer types (1). Moreover, this cancer is notoriously resistant to all conventional treatment modalities, including chemotherapy, radiotherapy, and even modern targeted therapies. The lack of effective treatment results from a poor understanding of PDAC tumor biology. Therefore, a better understanding of the aggressive characteristics of PDAC and tumorigenesis is needed before treatment advances can be made.

Recently, inflammation and other tumor microenvironment characteristics have drawn attention as central factors in the tumorigenesis of many cancers. The association between inflammation and PDAC development has been known for years (2, 3) and was recently validated in an animal model (4). Throughout the process of tumorigenesis, disease progression, and metastasis, the microenvironment of the local host tissue is an active participant and determines the extent of cancer cell proliferation, angiogenesis, invasion, and survival (5, 6). Treatments that target both the cancer and its surrounding microenvironment may provide the best approach (7, 8). This approach is particularly useful in PDAC, which is characterized by a dense tumor stroma that contains a cell-rich population, including stellate cells, fibroblasts, smooth muscle cells, endothelial cells, dendritic cells, macrophages, and other inflammatory cells. Tumor cells can release chemotactic factors that induce inflammatory cell infiltration. In turn, inflammatory cells can produce cytokines and growth factors that can directly enhance tumor growth or act on...
RasG12V mice were crossed with Ela-CreERT mice, which previously (4). Briefly, K-RasG12V was engineered following a loxp-GFP-stop-loxp cassette (cLGL-K-RasG12V). cLGL-K-RasG12V promoter (CAG) and blocked by the proximal insertion of a human cytomegalovirus and chicken -actin chimeric promoter (Kit w-sh/w-sh), ref. 18. We further assessed the clinical relevance by correlating mast cell infiltration with the survival of patients with PDAC. Our results indicate that targeting mast cells may be a promising novel therapy for PDAC.

Translational Relevance

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death, and no effective therapy is currently available for it. We have identified a previously undescribed role of mast cells in PDAC. Mast cells migrate to the tumor site and provide a microenvironment that allows for tumor progression. These results highlight the practical importance of mast cells in PDAC and indicate that targeting mast cells may be a promising novel therapy for PDAC.

Mast cells play a key role in PDAC tumorigenesis and the survival of patients with PDAC. Our results indicate that mast cells in the tumor microenvironment are essential for PDAC tumorigenesis. To test this hypothesis, we used a transgenic 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 investigated the contribution of mast cells to PDAC tumorigenesis by using a mast cell–deficient mouse model (Kit w-sh/w-sh, ref. 18). 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 PDAC tumorigenesis and present a novel therapeutic target.

Materials and Methods

Mouse models

K-RasG12V mutation mice were developed by our group (4). The K-RasG12V knockin mice have been described previously (4). Briefly, K-RasG12V was engineered following a human cytomegalovirus and chicken -actin chimeric promoter (CAG) and blocked by the proximal insertion of a loxp-GFP-stop-loxp cassette (cLGL-K-RasG12V). cLGL-K-RasG12V mice were crossed with Ela-CreERT mice, which targeted the expression of high levels of mutant K-ras in pancreatic acinar cells (4). C57BL/6 wild-type mice were obtained from The Jackson Laboratory, Bar Harbor, ME. Mast cell–deficient mice on a C57BL/6 background (Kit w-sh/w-sh) were gifts from Dr. Stephen E. Ullrich and from The Jackson Laboratory. The mice were housed in facilities approved by the Association for Assessment and Accreditation of Laboratory Animal Care International. The University of Texas MD Anderson Cancer Center Institutional Animal Care and Use Committee approved all the animal procedures described here (4, 19).

Immunohistochemical and histochemical staining with image analysis

Immunohistochemical studies were conducted using markers for inflammatory cells, including leukocytes (CD45), neutrophils (Gr-1), macrophages (F4/80), and mast cells, on 4-µm unstained sections from the human tissue microarray blocks and mouse pancreatic tissue blocks using a mouse monoclonal antibody against CD45 (Biocare Medical). To retrieve the antigenicity, we treated the tissue sections at 100°C in a steamer containing 10 mmol/L citrate buffer (pH 6.0) for 1 hour. The sections were then immersed in methanol containing 0.3% hydrogen peroxide for 20 minutes to block endogenous peroxidase activity and were incubated in 2.5% blocking serum to reduce nonspecific binding. The sections were then incubated for 1 hour at 37°C with anti-CD45 at a 1:50 dilution. Standard avidin–biotin immunohistochemical analysis of the sections was done according to the manufacturer’s recommendations (Vector Laboratories). Vector Red was used as a chromogen, and hematoxylin was used for counterstaining.

Toluidine blue staining (pH 2.0–2.5) for mast cells was carried out on continuous slides next to the slides stained for CD45.

The staining results were evaluated independently by 2 gastrointestinal pathologists to determine the percentage of positive cells in each core quantitatively with the Ariol Automated Image analysis system (Applied Imaging Corp.).

RNA extraction from pancreatic tissues in mice, cDNA microarray hybridization, and quantitative real-time reverse transcriptase PCR in superArray

Pancreatic tissues were selected according to different lesion stages in mice: normal pancreatic (NP) tissue from K-ras wild-type mice; bulk pancreatic tissue from K-rasG12V mice that had been morphologically confirmed as chronic pancreatitis (CP); bulk pancreatic tissue from K-rasG12V mice that had been morphologically confirmed as stage I, II, or III pancreatic intraepithelial neoplasia (PanIN) on a CP background; and bulk pancreatic tissue from K-rasG12V mice that had been morphologically confirmed as PDAC in a pool of CP. Total RNA was isolated from mouse tissue samples with TRizol reagent (Invitrogen) according to the manufacturer’s instructions. To determine the expression profile of K-rasG12V mice, we carried out RNA hybridization on cDNA microarrays with the MouseWG-6 Expression BeadChip Kit v2.0 (Illumina, Inc.). Expression was confirmed by 15 quantitative real-time reverse transcriptase PCR analyses conducted with a superArray kit (SA Biosciences).
Cell culture and adoptive intraperitoneal transfer of bone marrow–derived mast cells into Kit$^{Wsh/W-sh}$ mice for mast cell reconstitution and Panc-02 PDAC cell implantation

Panc-02 PDAC cells were cultured in RPMI-1640 containing 10% FBS. Bone marrow stem cells were isolated from the femurs and tibiae of 6-week-old C57BL/6 mice and then cultured at a concentration of $10^6$ cells per milliliter in complete RPMI-1640 supplemented with murine recombinant interleukin (IL)-3 (10 ng/mL; PeproTech) and stem cell factor (10 ng/mL; PeproTech). Nonadherent cells were transferred to fresh culture media twice per week for 4 to 5 weeks, at which point more than 98% of viable cells were mast cells, as verified by flow cytometry (CD45⁺CD117⁺FceR1⁺CD3⁻B220⁻) and positive staining for toluidine blue (19). A total of $1 \times 10^7$ bone marrow–derived mast cells per mouse was injected intraperitoneally into mast cell–deficient mice. Six weeks later, $2.5 \times 10^5$ Panc-02 PDAC cells were orthotopically implanted into the pancreas of each Kit$^{W-}$ mouse and wild-type C57BL/6 mouse. Another 2 weeks later, 5 mice from each group were euthanized every 7 days, and tumor sizes and weights were measured. An additional 15 mice were used for survival analysis.

Orthotopic PDAC mouse models

To carry out the intrapancreatic injection, we anesthetized mice with 2.5% tribromoethanol and made a 0.5- to 1-cm incision in the left subcostal region. Panc-02 PDAC tumor cells were injected into the caudal pancreas (20). The peritoneum and skin were closed with the EZ Clip Wound Closing Kit (Stoelting Co.). At 2 weeks after implantation, 5 mice from each group were euthanized every 7 days, and PDAC tumors were evaluated macroscopically for the presence of orthotopic tumors and metastases in the abdominal cavity (20). Tumor volumes were estimated using the following formula: $(r \times \text{long axis} \times \text{short axis} \times \text{short axis})/6$ (21). An additional 40 mice in each group were used for survival analysis.

Patients and tissue samples

We searched the patient record database at The University of Texas MD Anderson Cancer Center for patients with stage II PDAC who had undergone pancreaticoduodenectomy between 1990 and 2005 and had not received any form of preoperative chemotherapy or radiotherapy. Patients who had received preoperative chemotherapy or radiotherapy or had died from postoperative complications were excluded from our study. Our search identified 67 patients who met those criteria: 45 men and 22 women whose median age at the time of surgery was 63.7 years (range: 39.8–79.9 years). The patients’ follow-up information through August 2008 was extracted from the prospectively maintained institutional pancreatic cancer database managed in the Department of Surgical Oncology and, if necessary, updated by review of the U.S. Social Security Index. Overall survival was calculated as the time from the date of diagnostic biopsy or surgery (if biopsy was not diagnostic) to the date of death or the date of last follow-up if death did not occur. The median follow-up time was 27.5 months. We constructed tissue microarrays using formalin-fixed, paraffin-embedded archival tissue samples from our patient population. The Institutional Review Board of MD Anderson Cancer Center approved this study.

Archival tissue blocks and their matching hematoxylin and eosin (H&E)-stained slides were retrieved, reviewed, and screened by a gastrointestinal pathologist (H. Wang) to identify representative tumor regions and nonepithelial pancreatic parenchyma. For each patient, 2 cores of tumor tissue and 2 cores of paired benign pancreatic tissue were sampled from representative areas using a 1.0-mm punch. The tissue microarrays were constructed with a tissue microarrayer (Beecher Instruments) as described previously (22). The cutoff point of the mast cell score was 3.68 (i.e., 75th percentile of the mast cell score in the sample population).

Statistical analysis

The Student $t$ tests and one-way analysis of variance were used to compare quantification data. Survival probability curves were constructed with the Kaplan–Meier method, and the log-rank test was used to evaluate the statistical significance of differences.

Statistical analysis was conducted with Statistical Package for Social Sciences software (SPSS Inc.). We used a 2-sided significance level of 0.05 for all statistical analyses.

Results

Mast cell early infiltration and mast cell cytokine expression are associated with PDAC development in a transgenic spontaneous mouse model

To measure mast cell influx during the development of PDAC, we used a transgenic $K-ras^{G12V}$ mouse model that developed CP, PanINs, and invasive PDAC (4). In our study, CP was defined morphologically by the loss of acinar cells, fibrosis, and infiltration of inflammatory cells, including monocytes and lymphocytes, without evidence of 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 ($N = 4$) obtained from wild-type littermates served as controls. $K-ras^{G12V}$ mice had an early influx of inflammatory cells to the tumor microenvironment. The mast cell staining index scores for NP, CP, PanIN, and PDAC tissues were 5, 104, 83, and 58, respectively (Fig. 1). 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. Although mast cells were evenly distributed in CP and PanIN lesions, they accumulated at the infiltrating edges of the tumor. Because of this uneven distribution in PDAC, the mast cell score (normalized to the area of the whole pancreas) in some cases seemed lower in PDAC than in CP.
Mast cells in the tumor microenvironment are required for PDAC tumor growth in vivo

To determine the contribution of mast cells to the tumorigenesis of PDAC, we compared tumor growth in mast cell–deficient Kitw-sh/w-sh mice (Kit−/−/− mice) and syngeneic C56BL/6 mice (wild-type mice). When Panc-02 PDAC cells, a tumorigenic murine PDAC cell line derived from a methylcholanthrene-induced tumor growing in a male C57BL/6 mouse, were orthotopically implanted in the pancreas, the growth of tumor was significantly suppressed in mast cell–deficient Kitw-sh/w-sh mice compared with syngeneic C56BL/6 mice; only 20% of Kit−/−/− mice had measurable tumors 28 days after implantation compared with 100% of wild-type mice (P = 0.033; Fig. 2). The Kit−/− mice also had a lower incidence of hemorrhagic ascites than the wild-type mice.

Figure 1. Mast cell infiltration during PDAC development in K-rasG12V mice. A and E, few mast cells were found in NP tissue (200×). B and F, influx of mast cells in CP (200×). C and G, influx of mast cells in PanIN (200×). D and H, influx of mast cells in PDAC (200×). A–D, H&E staining. E–H, toluidine blue staining. Serial sections were stained with H&E and toluidine blue; mast cells were stained red-purple (metachromatic staining against a blue background). I, quantitative evaluation of mast cell infiltration in pancreatic tissues (score = the ratio of the total number of mast cells to the area of pancreas) during PDAC development. The P values for the comparison between CP, PanIN, and PDAC versus NP are as indicated. The P values for the comparison of PDAC versus CP and PDAC versus PanIN were all more than 0.5, showing no statistical difference.

Figure 2. Suppressed PDAC growth in mast cell–deficient mice. A, Panc-02 PDAC tumors were larger in wild-type (WT) C57BL/6 mice (left) than in mast cell–deficient Kitw-sh/w-sh mice (right). B, tumor growth in WT and Kitw-sh/w-sh mice implanted with Panc-02 cells. Growth in WT mice is shown in red, and growth in mast cell–deficient mice is shown in blue. C, survival curves of WT mice (red) and Kitw-sh/w-sh mice (blue) implanted with Panc-02 cells.
Kit repopulated with mast cells compared with the parental pancreases of Kit<sup>+/−</sup>, and as expected, no mast cells were found in the pancreases of Kit<sup>−/−</sup> mice (Fig. 4B, E, and H). Similar results were observed in a subcutaneous model with Panc-02 cells (data not shown).

To further confirm the hypothesis that mast cells promote PDAC tumorigenesis, we used a mast cell reconstitution mouse model. Bone marrow–derived mast cells from wild-type C57BL/6 mice were injected into mast cell–deficient Kit<sup>−/−</sup> mice and repopulated in the pancreatic tissues. Tumor growth was significantly increased in the Kit<sup>−/−</sup> mice repopulated with mast cells compared with the parental Kit<sup>−/−</sup> mice (P = 0.009; Fig. 3). Mast cell reconstitution also increased the incidence of hemorrhagic ascites to 50%. The repopulation of mast cells was confirmed by both H&E and toluidine blue staining (Fig. 4C, F, and I). These data support the critical role of mast cells in PDAC progression.

Mast cells infiltration predicts a worse prognosis of patients with PDAC

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. 5A–E). Patients with mast cell scores less than 3.68 survived significantly longer (median overall survival duration, 36.2 ± 9.4 months) than did patients with mast cell scores 3.68 or more (median overall survival duration, 13.4 ± 3.4 months; P = 0.008, high vs. low mast cell infiltration; Fig. 5f). In addition, the incidence of recurrence was lower in patients with mast cell scores less than 3.68 (67%) than in patients with mast cell scores 3.68 or more (100%; P = 0.003, the Fisher exact test.). In multivariate analysis (Supplementary Table), mast cell score is close to but does not reach statistical significance (HR: 1.88, 95% confidence interval (CI), 0.95–3.73, P = 0.07) after adjusting lymph node status. The lymph node metastasis is an independent prognostic factor for poor survival (HR: 2.31, 95% CI, 1.10–4.84 P = 0.03).

Discussion

In this study, we showed 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 K-rasG12V transgenic 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.

Mast cells are important in allergic and late-phase reactions, inflammation, and the regulation of adaptive T-cell–mediated immunity (23–25). However, the role of mast cells in the tumorigenesis of cancers is not totally clear, and data about their benefit or detriment to tumorigenesis have been controversial, depending on the local stromal conditions (26). On the one hand, mast cells may promote tumor development by (i) facilitating tumor angiogenesis through heparin-like molecules, and heparin could further permit neovascularization and metastasis through its anticoagulant effects (27); (ii) secreting histamine and growth factors, such as VEGF, platelet-derived growth factor, stem cell factor, and nerve growth factor, which may facilitate the proliferation of tumor cells; and (iii) contributing proteolytic components necessary for tumor invasiveness (28). On the other hand, mast cells could also be detrimental to tumor growth by secreting several cytokines, such as IL-4, and proteolytic enzymes that may induce the apoptosis of malignant cells (29). Consistent with the dual roles of mast cells in inhibiting or promoting tumor growth, high mast cell numbers represent a good prognostic indicator in breast cancer, non–small cell lung carcinoma, and ovarian cancer (16, 17), but they are associated with poor prognosis in skin cancer (both melanoma and nonmelanoma and Merkel cell tumors; refs. 13, 14), oral squamous cell carcinoma, several types of lymphoma, and prostate cancer (16, 17).

Inflammation is associated with an increased risk for most cancers. CP produces pancreatic inflammation and is associated with an increased risk of PDAC, thus establishing a link between cancer and inflammation on an epide miologic level (2, 3). To determine the role of mast cells in PDAC tumorigenesis, we first determined when and how much mast cells infiltrate the PDAC tumor microenvironment, using a K-rasG12V transgenic spontaneous mouse model (4). Activating K-RAS point mutations at codon 12 are
12 (from GGT to GAT or GTT, and more rarely, CGT) results in the substitution of glycine with aspartate, valine, or arginine. These mutations are the first known genetic alterations in PDAC, occurring sporadically in NP tissue, and are detected in approximately 30% of early neoplasms, with the frequency rising to nearly 100% in advanced PDAC (30, 31). PDACs nearly always arise from precursors that sustain activating K-RAS mutations, whereas such mutations are almost never seen in less common pancreatic cancers such as islet cell carcinomas (32, 33). Thus, the PDAC generated in this mouse model mimicked the tumorigenesis of human PDAC. Our results showed that mast cell infiltration was an early event and that mouse mast cells distributed into CP and mouse PanIN lesions but were rarely found in NP tissues. During the development of PDAC, mast cells accumulate to the tumor microenvironment. Using quantitative real-time reverse transcriptase PCR analysis, we noted that during the progression from NP to CP to PanIN to PDAC, many cytokines, particularly mast cell-related cytokines and receptors (e.g., CXCL5, IL-8rb, IL1β, and tumor necrosis factor) were consistently upregulated in the microenvironment during PDAC development in K-rasG12V mice (data not shown). These results suggest that mast cells migrate into the tumor microenvironment and play a critical role in PDAC development.

To assess the causative role of mast cells in PDAC tumorigenesis, we manipulated mast cells in vivo to document the necessity of mast cells for PDAC tumor growth. In Kitw-sh/w-sh mast cell–depleted mice, the growth of transplanted (both orthotopically and subcutaneously) tumors and incidence of hemorrhagic ascites were much lower than in wild-type C57BL/6 mice, and the survival of tumor-bearing Kitw-sh/w-sh mice was prolonged compared with tumor-bearing wild-type mice. These data indicate that mast cells are an important part of the tumor microenvironment for PDAC growth. When reconstituted Kitw-sh/w-sh mice intraperitoneally with bone marrow–derived cultured mast cells (BMCMC) from wild-type (Kit+/+) mice (wild-type BMCMC → Kitw-sh/w-sh mice; refs. 18, 34), the growth of mouse PDAC tumor and changes in the tumor microenvironment in this
reconstitution model recapitulated those found in wild-type mice, further supporting the hypothesis that mast cells support PDAC tumor growth and progression.

Furthermore, the observed role of mast cells in PDAC tumorigenesis in mouse models is also clinically relevant. Our results showed that high mast cell infiltration into the tumor microenvironment was predictive of poor clinical outcomes in patients with PDAC.

The exact mechanism by which mast cells contribute to PDAC development is not entirely clear and is beyond the scope of the current study. However, 2 recent studies and the data reported in this article yield valuable insights. Soucek and colleagues showed in a β-cell tumor model that activation of Myc in vivo triggered rapid recruitment of mast cells to the tumor site, a recruitment that is absolutely required for macroscopic tumor expansion and that treatment of established β-cell tumors with a mast cell inhibitor rapidly triggered hypoxia and cell death of tumor and endothelial cells (35). They observed that mast cell–induced angiogenesis was the key mechanism that

Figure 5. Association of mast cell infiltration with survival of patients with PDAC. No mast cells were found in NP tissues. A, 100× and D, 400×. B, a human PDAC tissue microarray was stained with toluidine blue. Mast cells were found in the human PDAC tumor microenvironment: (C) 100× and (E) 400×. 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 less than 3.68; lower curve, patients with mast cell scores 3.68 or more. The P value was derived using the log-rank statistic.
promoted the growth of pancreatic islet tumor cells. These data suggest that inhibition of mast cell function may prove therapeutically useful in restraining the expansion and survival of pancreatic and other cancers. In human PDAC, Strouch and colleagues (36) found that increased mast cell infiltration into the tumor site was correlated with poor patient survival. In addition, they showed that the mast cell–conditioned medium promoted tumor growth in vitro. Our findings confirm the observation that increased mast cell infiltration is associated with poor prognosis. Other studies in our group are under way to address the mechanism by which mast cells contribute to PDAC development.

In summary, we identified a previously undescribed role of mast cells in PDAC. Mast cells migrate to the tumor site and provide a tumor microenvironment that allows for tumor progression. These results highlight the practical importance of mast cells in PDAC and indicate that targeting mast cells may be a promising novel therapy for PDAC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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