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Targeting Tumor Stroma: A Novel Therapeutic Approach to Pancreatic Cancer Treatment

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The prognosis of Pancreatic Ductal Adenocarcinoma (PDAC) is extremely poor. The majority of the patients die within 6 months after diagnosis, and only 6% of the patients survive more than five years [1]. The major factors leading to this poor prognosis are the late stage at the time of diagnosis and the lack of effective therapies. Development of early detection methods and effective therapies for PDAC represents two important areas to improve the outcome of this highly lethal disease. Currently, surgical intervention for resectable diseases and gemcitabine-based systemic chemotherapies for advanced diseases have been the major options for pancreatic cancer patients. Unfortunately, over the last 30 years, while significant efforts have been made to improve the therapies, the five-year survival rate for pancreatic cancer has not improved significantly. Clearly, new therapeutic strategies are urgently needed to improve the outcome of this devastating disease.

Over the past decade, with the development of genomics and proteomics technologies, significant effort has been made in our understanding of the molecular biology and pathogenesis underlying PDAC, providing new hypotheses and approaches for developing targeted therapies directed against the signaling pathways of tumor cells in PDAC. However, the clinical trials of many of these various targeted therapies have had disappointing results, reflecting the complex nature of pancreatic tumorigenesis and its drug resistance. Drug resistance of pancreatic cancer might be related to highly complex molecular events, including drug resistance of pancreatic tumor cells, vasculature of the pancreatic cancer, tumor-stroma interactions and other mechanisms. A recent approach directed against cancer-associated stroma demonstrated an increase in therapeutic delivery of gemcitabine, resulting in an improvement of prolonged survival when co-administrated with systemic therapy [2]. This encouraging result suggests that the poor vascularization in pancreatic cancer tissue due to the prominent stroma surrounding tumor cells may in part contribute to the drug resistance of pancreatic cancer.

Tumor progression has long been defined as a multi-step process during which mutations accumulate in cancer cells. Until recently, efforts to develop new therapies have focused on targeting cancer cells. The importance of stroma in tumorigenesis was suggested decades ago, but only recently have investigators delved deep into the role that cancer-associated stroma plays in all stages of cancer including initiation, progression and metastasis. Accumulating evidence indicates that cancer cells can activate their surrounding stroma by multiple signaling pathways involving EGF, TGFβ1, and FGF. PDACs are notorious for their exuberant stroma; stroma can make up to 90% of the tumor mass that surrounds the tumor cells. In addition to being a barrier to intra-tumor perfusion, the dense stroma plays very important mechanistic roles in the progression of PDAC. The crosstalk of neoplastic cells and stromal components could stimulate the formation of reactive stroma; the reactive stroma in turn promotes cancer progression, invasion, metastasis and drug resistance. This evidence suggest that, in addition to tumor cell signaling pathways, the stroma of pancreatic cancer should be considered for development of new therapeutic approaches. Therefore, targeting tumor stroma in combination of chemotherapy represents a novel strategy for PDAC treatment. Several recent studies have started to develop novel therapies targeting tumor stroma of PDAC, including cancer associated fibroblasts, immune cells, pancreatic stellate cells and Extracellular Matrix Components (ECM).

Targeting Cancer Associated Fibroblasts

Sonic hedgehog signaling is known to be a major pathway leading to stromal activation. A study published in 2009 reported that targeting the sonic hedgehog pathway resulted in significant depletion of cancer associated stroma in a genetically engineered mouse model of PDAC [2]. Combination therapy using gemcitabine and a hedgehog pathway inhibitor produced a transient increase in intratumoral vascular density and improved delivery of gemcitabine.

Targeting Immune Cells

An immunosuppressive microenvironment is predominantly developed during PDAC progression. Overcoming such tumor-induced immune suppression could potentially invoke antitumor immunity and improve treatment outcomes in PDAC. Activation of tumor associated macrophages by CD40 agonists has been demonstrated to be effective in depletion of tumor stroma and shown efficacy against PDAC in human and a genetically engineered mouse model [3]. CD40-activated macrophages could rapidly infiltrate tumors, become tumoricidal, and facilitate the depletion of tumor stroma [3].

Targeting Pancreatic Stellate Cells

Ellagic acid is a plant-derived polyphenol found in a wide variety of fruits and nuts that has anti-oxidant, anti-inflammatory and anti-fibrosis properties [4] and this phenol has been shown to block the activation of pancreatic stellate cells [5]. *In vivo,* ellagic acid reduced pancreatic inflammation and fibrosis when administered orally to ten week old male Wistar Bonn/Kobori rats, an experimental model of spontaneous chronic pancreatitis, for ten weeks [6]. Ellagic acid inhibited the production of reactive oxygen species in pancreatic stellate cells in response to transforming growth factor-beta1 (TGF beta 1) or platelet-derived growth factor (PDGF) in this animal model.

Targeting ECM

In the two studies published earlier this year, hyaluronan was

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found to be an abundant component in the ECM of both human and murine pancreatic cancer tissues [7,8]. The authors from Cambridge showed that depletion of hyaluronan by PEGPH20, a PEGylated human recombinant PH20 hyaluronidase, induced the re-expansion of PDAC blood vessels and increased the intratumoral delivery of two chemotherapeutic agents, doxorubicin and gemcitabine. The enzyme also triggered fenestrations and interendothelial junctional gaps in PDAC tumor endothelia and promoted a tumor-specific increase in macromolecular permeability [7]. Combination therapy with PEGPH20 and gemcitabine prolonged survival over gemcitabine monotherapy in a genetically engineered mouse model of PDAC [7] as well. In a separate study from Seattle, the authors showed that enzymatic degradation of hyaluronan results in a rapid reduction of interstitial fluid pressures accompanied by the appearance of widely patent functioning vessels in mouse model of PDAC [8]. Combination therapy with PEGPH20 and gemcitabine resulted in permanent remodeling of the tumor microenvironment and consistent tumor responses, and nearly doubled overall survival [8]. In light of the results from these two studies, clinical trials have been initiated to test the strategy of depleting hyaluronan in patients with pancreatic cancer.

With the recognition of the crucial role of tumor stroma plays in cancer progression and therapy improvement, researchers have started implementing the concept into new therapeutic strategies for the treatment of PDAC. Stroma components, including cancer associated fibroblasts, pancreatic stellate cells, extracellular matrix components (ECM), and immune cells, are potential targets for exploration. It is anticipated that innovative strategies targeting stroma could result in more effective therapies against pancreatic cancer.

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References

1. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62: 10-29.
2. Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, et al. (2009) Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science 324: 1457-1461.
3. Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, et al. (2011) CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. Science 331: 1612-1616.
4. Priyadarsini KI, Khopde SM, Kumar SS, Mohan H (2002) Free radical studies of ellagic acid, a natural phenolic antioxidant. J Agric Food Chem 50: 2200-2206.
5. Masamune A, Satoh M, Kikuta K, Suzuki N, Satoh K, et al. (2005) Ellagic acid blocks activation of pancreatic stellate cells. Biochem Pharmacol 70: 869-878.
6. Suzuki N, Masamune A, Kikuta K, Watanabe T, Satoh K, et al. (2009) Ellagic acid inhibits pancreatic fibrosis in male Wistar Bonn/Kobori rats. Dig Dis Sci 54: 802-810.
7. Jacobetz MA, Chan DS, Neesse A, Bapiro TE, Cook N, et al. (2012) Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut
8. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, et al. (2012) Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21: 418-429.