Subtypes of pancreatic stellate cells and distant metastasis of pancreatic ductal adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC) is now the third most leading cause of cancer-related mortality in the USA (1), and the 5-year survival rate is mere 9% (2). Although surgical resection might be potentially curative therapies for some early patients with PDAC, the recurrence rate is quite high, with the median overall survival varies between 24–30 months (1) and the 5-year survival rate of resected patients is only about 20% (3). In addition to a few cases, monotherapy with immune checkpoint inhibitors, targeted monoclonal antibodies or receptor tyrosine kinase-targeted therapies have been showed ineffective in the clinical treatment for this disease (4).

The poor prognosis of PDAC is mainly due to inefficient diagnosis and tenacious drug resistance. The extracellular matrix (ECM), as the main component of the PDAC stroma, provides biophysical and biochemical cues to regulate malignant cell behavior (5). Abnormal ECM in the tumor microenvironment prompts cancer progression by promoting cellular transformation and metastasis, influences stromal cell behaviors, such as inflammation and angiogenesis, and can intensify the formation of a tumorigenic microenvironment (6). ECM proteins have also been regarded as significant part of the metastatic niche to enable the growth of the metastasis-initiating cells (7). In the normal pancreas, pancreatic stellate cells (PSCs) account for 4% of the total number of cells, and are mainly located around the acinus and interlobular space of the pancreas (8). PSCs are the major constitutive component of pancreatic cancer stroma. Pancreatic cancer cells (PCCs) release mitogenic and pro-fibrogenic stimulators, which can lead to the activation of PSCs (9). The activation of PSCs and the development of dense stroma are prominent features of PDAC, which illustrates the aggressiveness of PDAC (10,11). Activated PSCs secrete a variety of cytokines that regulate the tumorogenesis, metastasis and chemotherapy resistance of pancreatic cancer (12). The interaction between PSCs and PCCs not only promotes tumor progression and metastasis, but also maintains PSCs activation, and results in a vicious cycle which intensifies PDAC tumorigenesis and drug resistance (13-18).

All in all, the outcomes for PDAC remain dismal and new therapies are urgently needed (1). To date, it is still obscure whether PSCs regulates the progression of PDAC, we tend to believe that figure out the communication between PSCs and PCCs could contribute to develop early detection methods and novel therapeutic options for PDAC.

The pancreatic stromal TGFβ regulates tumor-related PSCs and accelerates the development of PDAC. Briefly, by secreting TGFβ1, tumor cells mediate the conversion of fibroblasts into myofibroblasts, which in turns promote the migration, invasion and epithelial-mesenchymal transition (EMT) of tumor cells. Chemokines are a family of proteins with low molecular weight, which can attract leukocytes (such as monocytes and neutrophils) from blood circulation to the infected or damaged site, and they are believed to
play fundamental roles in various biological processes including inflammation, angiogenesis, immune response and so on. CXC family chemokines is critical responsible for the cellular biological roles mentioned above (19). Among them, CXCL1 and its receptor CXCR2 are highly expressed in PCC lines and pancreatic cancer tissues (20). The specific molecular mechanism leading to PDAC metastasis is still unknown. Some key signaling pathways, for example, PI3K/Akt signaling pathways, substantially contributes to regulate cell proliferation, apoptosis, angiogenesis, immune suppression, invasion, and metastasis (21). High level of Akt expression can induce EMT and enhance the invasion and metastasis ability of squamous cell carcinoma. Additionally, Akt signaling mediates tumor necrosis factor (TNF)-enhanced endothelial cell migration and tumor angiogenesis (22).

In this Journal, Zhang et al. explored the interaction between PSCs and PCCs, and elucidated the relationship between fibroblast activation protein α-positive (FAPα+) PSCs and the clinicopathological characteristics of PDAC. What's more, the authors discussed the effects of FAPα+ PSCs in PDAC and the underlying mechanism.

By performing tissue microarray analysis, the author found that FAPα was mainly expressed in the PSCs. The higher number of FAPα+ PSCs predicts a higher lymph node metastasis and poorer survival. PCCs can release TGFβ1 and induce PSCs to express FAPα. The authors further explored the effects of FAPα+ PSCs on the biological behavior of PDAC in vitro and in vivo. Cytokine chips was performed to measure the differential expression of cytokines in FAPα+ and FAPα-PSCs. In addition, the phosphotyrosine kinase receptor protein chip was used to detect the phosphorylated tyrosine kinase receptors. Finally, immunoprecipitation method was used to detect the interaction between differential cytokines and tyrosine kinase receptors. They found that, compared with FAPα- PSCs, FAPα+ PSCs exerted greater potential to promote the migration, invasion and metastasis of PCCs. Additionally, FAPα+ PSCs secreted considerable amount of CXCL1, which binds to CXCR2 and activates the tyrosine kinase receptors EphB1 and EphB3 in PCCs, results in phosphorylation of the downstream Akt and finally promotes the migration and invasion of PCCs. What's more, an FAPα inhibitor named talabostat (PT100) could inhibit the effects of FAPα+ PSCs on PCCs and PDAC. This is the first study that reveals the interaction between FAPα+ PSCs and PCCs, and elucidates their role in PDAC progression.

FAPα is a kind of membrane serine peptidase that belongs to the type II serine protease family, thus FAPα has the proteolytic activity and can mediate the cleavage of some peptides and cytokine receptors (23). Studies have shown that FAPα is selectively expressed in fibroblasts in the malignant stroma (24), and the proteolytic activity endows FAPα to promote tumor cells growth and metastasis (25).

Notably, the authors have demonstrated that FAPα+ PSCs play a significant role in the migration, invasion, and metastasis of PDAC through Akt signaling pathway, which also indicates a new mechanism that FAPα+ PSCs interact with PCCs. Collectively, this study has revealed the molecular mechanisms underlying the cell biological functions of FAPα+ PSCs and the interaction between FAPα+ PSCs with PCCs, which shed light on a therapeutic target for PDAC treatment.

Actually, TGF-β1, which was mentioned in this paper, has been considered as one of the most important cytokines and plays a vital role in regulating the invasion and metastasis of the advanced tumors. For example, in the classic TGFβ-TβR-Smads pathway, TGF-β activates TGFβ I, and TGFβR I phosphorylates downstream R-Smads (Smad2 and Smad3). R-Smads combines with Co-Smad (Smad4) to form a complex and enters the nucleus and which in turn affects transcription and cell movement. Another classic pathway is TGFβ-TβR-TAB1/TAK1-MKK3-p38. In addition to these two pathways, TGF-β can also affect the expression of transcription factors such as Snail1/2, Slug, ZEB1/2, and HMGA2 through TRAF6, MKK3-p38. In addition to these two pathways, TGF-β can also promote tumor development and metastasis by affecting the tumor microenvironment. All these indicate that TGFβR is a potential tumor treatment target.

The TGF-β1 signaling is eliciting increasing attention in cancer therapy. TGFβ1 primarily binds to the type II receptor (TβR II), and then the complex recruits type I receptor (TβR I or ALK5), and subsequently activates the canonical TGF-β1 signaling by phosphorylating the receptor associated Smads. In recent years, several therapeutic approaches have been tried to target the TGF-β1 signaling, among which, several TGF-β1 inhibitors targeting TGF-β1 receptors have reached the clinics. For example, galunisertib (LY2157299) is an ALK5 inhibitor which has been investigated as a single drug or in combination with Gemcitabine. In addition, Vactosertib is a newly developed ALK5 inhibitor which is also investigated in clinical trial (ClinicalTrials.gov Identifier: NCT04258072). Thus, we might develop therapeutic
approaches according to the results of these clinical trials. Besides, it is also worthy to investigate the effect of FAPα in PSCs by direct FAPα knock in. That’s what we suggest the authors to do in the future research direction of TGFβ1. In this way, we might develop effective therapeutic target to control distant metastasis of PDAC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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