Chemotherapy and tumor microenvironment of pancreatic cancer

Qiaofei Liu, Quan Liao* and Yupei Zhao*

Abstract
Pancreatic cancer is an extremely dismal malignance. Chemotherapy has been widely applied to treat this intractable tumor. It has exclusive tumor microenvironment (TME), characterized by dense desmoplasia and profound infiltrations of immunosuppressive cells. Interactions between stromal cells and cancer cells play vital roles to affect the biological behaviors of pancreatic cancer. Targeting the stromal components of pancreatic cancer has shown promising results. In addition to the direct toxic effects of chemotherapeutic drugs on cancer cells, they can also remodel the TME, eventually affecting their efficacy. Herein, we reviewed the following four aspects; (1) clinical landmark advances of chemotherapy in pancreatic cancer, since 2000; (2) interactions and mechanisms between stromal cells and pancreatic cancer cells; (3) remodeling effects and mechanisms of chemotherapy on TME; (4) targeting stromal components in pancreatic cancer.

Keywords: Pancreatic cancer, Tumor microenvironment, Chemotherapy, Myeloid derived suppressor cells, Tumor associated macrophages, Pancreatic stellate cells, Cancer associated fibroblasts

Background
Pancreatic cancer is always referred to pancreatic ductal adenocarcinoma (PDAC) which is the fourth leading cancer death in USA. Its recent 5-year overall survival of pancreatic cancer is only 7.7% and its median survival time is about 6 months [1]. Chemotherapy is one of the most important treatments for patients with advanced pancreatic cancer. Several clinical advances of chemotherapy have been achieved by high quality, large scale, prospective and randomized clinical trials. Adjuvant chemotherapy based on gemcitabine or fluorouracil have shown promising effects to improve the overall survival [2, 3]; oral fluorouracil, S-1, has been reported to show better results than gemcitabine [4]; palliative FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) regimen was reported to be the best choice for patients with metastatic pancreatic cancer [5]. For some selected borderline or local unresectable pancreatic cancer, neoadjuvant chemotherapy have also been initially adopted, with the hope to lower down the tumor and regain the radical resection opportunities [6, 7].

Increasing interests have been put into approaches targeting the tumor stroma of pancreatic cancer. The TME of pancreatic cancer is characterized by dense desmoplasia and extensive immunosuppression [8]. Pancreatic stellate cells (PSCs) and cancer associated fibroblasts (CAFs) are the main matrix-producing cells in TME of pancreatic cancer [9]. Tumor associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs) are the most infiltration populations of immunosuppressive cells in the TME [10]. The network consisting of stromal cells and cancer cells has become to be the most shining star in the research field of pancreatic cancer. Targeting the stromal components has also shown primary positive results in pancreatic cancer [11–14].

Interactions between chemotherapy and TME have also been paid more and more attentions. On one hand, chemotherapy can induce immunogenic cell death (ICD) in certain tumors, which could potentially activate immune system. On the other hand, these chemotherapeutic drugs can also remodel the TME. Gemcitabine was reported to inhibit the expansion of MDSCs [15], however, it was also reported to induce T helper 2 (Th2)
cytokine environment in TME which induce the polarization of M2 polarized TAMs [16]. After gemcitabine treatment, pancreatic cancer secreted more GM-CSF, recruiting MDSCs to diminish the efficacy [17]. Cisplatin or carboplatin increased the potency of tumor cell lines to secrete interleukin (IL)-6 and prostaglandin E2 (PGE2) to induce IL-10-producing M2 polarized TAMs [18].

Four aspects focusing on the chemotherapy and TME of pancreatic cancer were reviewed in this paper, including: clinical landmark advances of chemotherapy in pancreatic cancer, since 2000; interactions and mechanisms between the stromal cells and pancreatic cancer cells; remodeling effects and mechanisms of chemotherapy on TME; targeting of the stromal components in pancreatic cancer.

The advances of chemotherapy in pancreatic cancer, since 2000

In respect of adjuvant chemotherapy, in 2001 and 2004, two papers substantially demonstrated that fluorouracil based adjuvant treatment improved overall survival, however chemoradiotherapy showed no survival benefits [2, 19]. In 2007, Oettle et al. [20] reported postoperative gemcitabine improved the estimated disease free survival at 3 and 5 years. In 2010, Neoptolemos et al. reported adjuvant use of fluorouracil plus folinic acid had comparable results with gemcitabine [3]. In 2013, adjuvant use of gemcitabine was reported to improve the 5-year overall survival and 10-year overall survival [21]. In 2016, Uesaka et al. revealed that adjuvant use of oral fluorouracil (S-1) achieved 44.1% of 5-year overall survival. Recently, Neoptolemos et al. [22] reported that the combinational use of gemcitabine with capecitabine prolonged the median survival of patients with resected pancreatic cancer.

In 2011, Conroy et al. [5] reported that for the patients with metastatic pancreatic cancer, FOLFIRINOX regimen significantly improved the results compared with gemcitabine alone. FOLFIRINOX improved median progression-free survival (PFS) and overall survival compared with gemcitabine alone. In 2013, the combination of nab-paclitaxel with gemcitabine was reported to significantly increase the response rate, improved PFS and overall survival among patients with metastatic pancreatic cancer, compared to gemcitabine alone [23]. In 2014, OFF (oxaliplatin, folinic acid and fluorouracil) was demonstrated to have better results than FF (folinic acid and fluorouracil) alone in patients with advanced gemcitabine refractory pancreatic cancer [24]. In 2016, Wang-Gillam et al. [25] reported nanoliposomal irinotecan in combination with fluorouracil and folinic acid significantly extended survival in patients with metastatic pancreatic cancer who previously received gemcitabine based therapy.

Theoretically, neoadjuvant therapy has several potential advantages over adjuvant therapy including better drug absorption, assessment of response, improved resectability rate and increased margin-negative resection rate [26]. However, the effects of neoadjuvant therapy in pancreatic cancer have not been confirmed. In 2010, a meta-analysis, mainly based on retrospective data, reported that approximately 30% of initially non-resectable tumor patients would be expected to have resectable tumors after neoadjuvant therapy, with comparable survival as initially resectable tumor patients [26]. In 2015, Ferrone et al. [6] reported neoadjuvant FOLFIRINOX for the patients with borderline resectable pancreatic cancer, resulted in a significant decrease in tumor size, lower morbidity, lymph node positivity, perineural invasion and overall survival. For the patients with resectable pancreatic cancer, due to the consideration of the risk of disease progression after neoadjuvant treatment, the clinical trials of neoadjuvant treatment is considered to be difficult and some perspective clinical trials were terminated early due to slow recruiting [7]. (The chronological list of clinical landmark events of chemotherapy in pancreatic cancer from 2000 is shown in Additional file 1: Table S1).

Interactions and mechanisms between stromal cells and pancreatic cancer cells in TME

Pancreatic cancer is a well-known inflammatory malignance. It has exclusive pathological characteristics, with an extensive desmoplastic stroma and immunosuppressive environment, comprised of abundant cellular components, mainly including PSCs, CAFs, TAMs and MDSCs. The cancer cells only consist of approximately 10–30% of the cellular components. Interactions between the cancer cells and the TME components facilitate tumor initiation, progression, metastasis and resistance to chemotherapy by various of mechanisms. Herein, we summarized eight potential tumor-supporting mechanisms contributing to the malignant behaviors of pancreatic cancer, through the interactions between cancer cells and the stromal cells in TME, including: (1) maintenance of pancreatic cancer stem cells (PCSCs); (2) modeling of the extracellular matrix (ECM); (3) promotion of the proliferation and survival of cancer cells; (4) promotion of the migration of cancer cells; (5) promotion of epithelial–mesenchymal transition (EMT); (6) promotion of the angiogenesis; (7) promotion of lymphangiogenesis; (8) induction of immunosuppressive reactions.

PSCs

More than 80% of the human pancreatic cancer tissue is the highly desmoplastic stroma. The principal cells responsible for the production of this stroma are PSCs in pancreatic cancer. In the healthy pancreas, the PSCs...
are always in quiescent status. These qPCSs have stellate shape and express desmin, nestin, vimentin, and glial fibrillary acid protein (GFAP) and exhibit abundant vitamin A containing lipid droplets in their cytoplasm. When activated, they will lose lipid droplets and develop a spindle-shaped morphology, express α-smooth muscle actin (α-SMA), proliferate, migrate, and secrete excessive amount of ECM proteins, leading to the imbalance between ECM production and degradation and eventually extensive desmoplasia.

A large number of interleukins (IL-1, IL6 and IL10), chemokines (C-X3-C motif chemokine ligand 1, CX3CL1) growth factors (e.g., vascular endothelial growth factor, VEGF; platelet-derived growth factor, PDGF; transforming growth factor beta, TGFβ) and tumor necrosis factor alpha (TNFα), have been identified to activate qPSCs [27]. Recently, Bhatia et al. [28] reported that pancreatic parathyroid hormone related protein (PTHrP) secreted by islet cells can also activate qPSCs. The aPSCs can proliferate, migrate to the injured location, with expression of α-SMA, changes of morphology and secretion of ECM proteins. These different processes are controlled and regulated by varieties of signal pathways (Table 1) [9]. The PSCs may be even activated at the pretumoral lesions and reciprocally promote carcinogenesis. Pando et al. [29] reported that a distinct stromal reaction and aPSCs around pancreatic intra-ductal neoplasia (PanIN) lesions which led to pancreatic cancer in a pancreatic cancer murine model overexpression KrasG12D. Cocultured with PanIN cells isolated from KrasG12D mice significantly increased proliferation, activation and ECM production of PSCs [30].

Some subpopulations of PSCs have been reported to have different roles in pancreatic cancer. Ikenaga et al. reported that the frequency of CD10 expression by PSCs was markedly higher in tumor tissue than in normal tissue (33.7% versus 0%). CD10(+) PSCs was associated with positive nodal metastases and a shorter survival time. These CD10(+) PSCs secreted more MMP3 and increased the invasion and growth of pancreatic cancer cells [31]. Fujiwara et al. [32] reported that CD271(+) PSCs seemed to appear at the early stage of pancreatic carcinogenesis and that CD271 expression was significantly correlated with a better prognosis in patients with pancreatic cancer.

CAFs

CAFs are also the main source of the collagen-producing cells in varieties of cancers. Unlike the stellate cells, which are exclusively located in liver and pancreas, CAFs are widely located in many normal tissue and tumor tissues. Many markers have been proposed to detect CAFs in different tissues, including α-SMA, tenascin-C, fibroblast activation protein (FAP), thy-1 (CD90), podoplanin, vimentin, fibronectin, type I collagen, prolyl4-hydroxylase, and fibroblast specific protein-1 (FSP-1)/S100A4 [33–35]. However, none of these markers are exclusively expressed on CAFs. A combination of morphological appearance and a marker definition are the most reliable methods to detect CAFs. CAFs in pancreatic cancer are another main effector cell population contributing to the desmoplasia. The origins of CAFs in pancreatic cancer include resident fibroblast, bone marrow derived cells, and PSCs [36]. Resident fibroblasts express α-SMA but do not express neural markers, such as nestin and GFAP, which is different from PSCs. After injuries of pancreas, inflammatory cytokines and chemokines from inflammatory cells, endothelial cells, or cancer cells activate resident fibroblasts and they proliferate and differentiate into CAFs [37, 38].

High intratumoral infiltration of several subtypes of CAFs, such as podoplanin, FAP or CD90 positive CAFs, predicted poorer prognosis of colon cancer, breast cancer, lung cancer and prostate cancer [35, 39-41]. Although the tumor-promoting roles of CAFs have been widely recognized, some studies also reported the tumor suppression by CAFs. In early stage of colon cancer, secretion of TGF-β by CAFs suppressed tumor initiation, however, TGF-β promoted cancer development in the advanced stage [42]. Flaberg et al. [43] reported that CAFs inhibited proliferation of cancer cell lines in vitro. Podoplanin-expressing CAFs inhibit growth of small cell lung cancer cells possibly under direct contact [44]. The dual roles of CAFs may be cancer cell type-dependent and may be changeable during the different stages of cancer.

TAMs

Inflammation is now a well-recognized hallmark of varieties of malignancies and pancreatic cancer is one of the

| Table 1 The signal pathways to regulate the biological behaviors of PSCs |
|---------------------------------------------------------------|
| **Proliferation** | **Migration** | **ECM production** |
| Hedgehog | + | |
| JAK-STAT | + | |
| MAPK | + | + |
| PI3K | + | + |
| PKC | + | |
| Rho kinase | + | |
| Smads | + | |
| Wnt/β-catenin | + | |
| PPAPy | + | |
| TF(AP-1, NK-xB, Gli-1) | + | + | + |
most well-known inflammatory cancers. In a cancerogen, DMBA (dimethylbenzanthracene)-induced murine pancreatic cancerogenesis model, with the progression of tumor initiation, the proportion of CD45 positive inflammatory cells rising from 15.5% in normal pancreatic tissue, to more than 50% in tumor tissue. The percentages of MDSCs, TAMs and the ratio of M2/M1 were significantly elevated with the progression of pancreatic cancerogenesis, in contrast, the percentages of helper T cell and cytotoxic T cell were significantly decreased. TAMs were one of the prevalent inflammatory cells in the TME [10, 45].

It is generally believed that tissue macrophages originate from circulating monocytes which extravasate into the tissues and then differentiate into mature macrophages, under the inductions of the tissue signals. However, recent studies showed that besides of the circulating monocytes, tissue resident macrophages can originate from yolk sac and fetal liver [46]. Most of the resident macrophages in skin, spleen, pancreas, liver and peritoneum cavity originate from yolk sac progenitors or fetal liver and are maintained independent from circulating monocytes. However, resident macrophages in gut only originate from circulating monocytes, and the resident macrophages in lung and kidney have dual origins [47, 48]. In contrast, macrophages involved in pathological responses appear to mainly come from circulating bone marrow derived monocytes [49]. Variable soluble factors have been reported to recruit the monocytes rom peripheral blood. Colony stimulating factor-1 (CSF-1) is abundantly expressed by many tumor cells and their stromal cells in TME. Tumor microenvironment-derived CSF-1 is the mast regulator of recruitment and differentiation of circulating monocytes, and knockout of CSF-1R showed depletion of TAMs [50, 51]. Another CSF-1R, IL-34 also showed to recruit TAMs [52]. In a xenograft model of skin cancer, VEGFA recruited monocytes to differentiate into TAMs [53]. Some chemokines, including CCL2, CCL18, CCL9, were reported to recruit the ly6c(+) monocyte into the tumor microenvironment in murine breast cancer and colon cancers [54–56]. Angiotensin-II was found to be responsible for the amplification of the self-renewing progenitor cells and hence the production of TAMs [57].

Plasticity and diversity are hallmarks of TAMs. Once the circulating monocytes are recruited into the tumor microenvironment, they will be induced to diverse phenotypes by various signals, including hypoxia, metabolic products, tissue damage, growth factors, cytokines, and chemokines. TAMs secrete varieties of cytokines, chemokines, poly-peptide growth factors, hormones, MMPs and metabolites, most of which possess tumor-promoting activities [58–60]. Description of macrophage activation has been currently contentious and confusing. In 1990s, differential effects of IL-4 or IL-13 compared to IFN-γ and/or lipopolysaccharide (LPS) on macrophage gene expression were described. The macrophages activated by IL-4 or IL-13 were termed to be “alternative activation,” and the ones activated by IFN-γ and/or LPS were termed to be “classical activation” [61]. Mill et al. proposed the terminology M1 for classical activated macrophages, and M2 for alternative activated macrophages in 2000 [62]. M2 was further defined into M2a, M2b, M2c for different activation scenarios [63]. Diversity of terminology of macrophages activated by different signals have impeded researches significantly. To tackle this issue, an international consensus nomenclature system was proposed in 2014 [64]. M1- and M2-polarized TAMs are only extremes of a continuum in a universe of functional states and most of the TAMs are in the continuum changeable status between M1 and M2 [65]. Activation of TAMs from tumor microenvironment of various tumors include hypoxia [66, 67], metabolic products of cancer cells (e.g., lactic acid) [59, 68], COX-2 [69], cytokines (e.g., TGF-β, CSF-1, GM-CSF), interleukins (IL-4, IL-10, IL-13) and plasma cells and immune complexes, damage associated molecular patterns (DAMPs), such as high-mobility group box1 protein (HMGB1), extracellular ATP, and degraded extracellular matrix components produced by cancer cells or stromal cells [70]. Signal pathways involved in M1 polarization include NF-Kappa B, STAT1, and IRF5, whereas IRF4, STAT6, MYC, PPARγ and KLF4 have been reported to promote M2 polarization [46, 65, 71]. Once activated, TAMs exert different functions to affect the malignant behaviors of cancers, which predominantly promote the invasiveness of cancer cells. The high infiltrations of TAMs, especially the M2 polarization TAMs, in tumor tissue predicted poor prognosis of many cancers, including pancreatic cancer.

**MDSCs**

The phenomenon that tumor can induce myelopoiesis has been observed for more than 100 years [72]. During myelopoiesis, various immature myeloid cells were generated, which lack of expressions of specific terminated markers for T cells, B cells, dendritic cells, NK cells and macrophages, and for a long time, these cells were called null cells. In 1960s, these cells were reported to induce a leukaemoid reaction which promoted tumor growth [73]. For a long time, owing to the phenotypic heterogeneity without a consensus regarding the cellular phenotype of these cells, diverse nomenclature, including immature myeloid cells (iMCs), myeloid suppressor cells (MSCs) and GR1(+) myeloid cells were recommended. Until 2007, a consensus reached to nominate MDSCs as the term for these cells [74].
In mice, MDSCs are generally defined as GR-1(+) CD11b(+) cells. And further, the murine MDSCs consist of two subgroups with different mononuclear and polymorphonuclear morphology and surface markers. Polymorphonuclear MDSCs (PMN-MDSCs) are referred to CD11b(+)Ly6C(low)Ly6G(+) cells and mononuclear MDSCs (M-MDSCs) were referred to CD11b(+) Ly6C(high)Ly6G(−) cells and M-MDSCs have potential to differentiate into terminated macrophages and dendritic cells. More than 80% of MDSCs are PMN-MDSCs [75, 76].

In humans, the definitions of human MDSCs are more complicated. Historically, human MDSCs were defined as lineage markers and HLA-DR(−), and CD33(+), CD14(+), CD15(−), CD11b(−), and CD14(−)CD15(+) cells. As well, PMN-MDSCs represent majority of the MDSCs in human cancer patients [77, 78].

It should be noted that in the bone marrow of normal mouse, there are also some cells with identical phenotype of MDSCs, however these cells do not have immunosuppressive capacities. So, MDSCs should also be activated to exert functions. Theory of “two sets of signals” has been proposed for the expansion and activation of MDSCs. The first set of signals promotes the expansion of MDSCs from bone marrow, and the second set of signals activates MDSCs [79]. The first set of these signals are regulated largely by GM-CSF, M-CSF, G-CSF, and other growth factors produced by tumor cells and macrophages [80, 81]. Then the second set of signals activate MDSCs, mainly by prostaglandin E2(PGE2), IL-1β, IL-4, IL-6, IL-10, IL-13, VEGF and TGF-β [82–85]. Recent studies reported that HMGBl and PPARy can also activate MDSCs by activation of STAT3, NF-κB, Erk1/2, and p38 signal pathways. Members of the STATS (STAT3, STAT5, and STAT6) have been considered to be critical factors in the regulation of MDSCs expansion and activities [86–88]. The downstream targets include S100A8, S100A9 and C/EBPβ [89]. Some chemokines are involved in the recruitment of MDSCs into tumor tissue. CXCL1, CXCL2, and CXCL5 have been shown to recruit MDSCs by binding to CXCR2. CXCL12 can also recruit MDSCs, by binding to CXCR4 [90].

After the process of expansion, recruitment and activation, in addition to immunosuppression, MDSCs exert various functions to promote the initiation, progression, and metastasis of cancers. Many mechanisms of immune suppression induced by MDSCs have been proposed, including production of ARG1, iNOS, IL-10, TGF-β, COX2 and induction of Tregs [90]. M-MDSCs and PMN-MDSCs were reported to exert different mechanisms of immune suppressions. M-MDSCs can suppress both antigen-specific and nonspecific T cell responses and show stronger suppressive activities than PMN-MDSCs. M-MDSCs exert immunosuppression through production of NO, however, PMN-MDSCs mainly depended on ROS. Both of them use ARG-1 for their suppressive activities [76, 91]. Peroxynitrite (PNT), the production of NO and superoxide, can inhibits T cells by nitrating T cell receptors (TCRs) which reduces their binding to cognate antigen-MHC complexes [92]. Depletion of L-arginine and cysteine by ARG-1 caused by MDSCs resulted in decreased CD3ζ chain expression, leading to reduction of IL-2 and IFN-γ to inhibit T lymphocyte proliferation. Several studies also showed that M-MDSCs could induce or recruit FOXP3+ Treg cells by different mechanisms, including production of TGF-β, CCR5 and ARG-1 [93, 94]. MDSCs have also been suggested to have a role in tumor angiogenesis in some tumors [95, 96]. Hypoxia can promote MDSC migration into tumor site via HIF-1α-induced production of chemokines and the recruited MDSCs will secret VEGF, basic fibroblast growth factor (bFGF) through activation of STAT3 to promote angiogenesis [97]. Bombina variegata peptide8 (Bv8) can also be induced by STAT3 to promote angiogenesis then enhance lung metastasis [98]. MDSCs were also reported to secret MMP-9 to promote tumor angiogenesis [90]. PMN-MDSCs produced HGF and TGF-β to induce EMT of primary melanoma cells. MDSCs can induce cancer stem cells of ovarian cancer by upregulation of microRNA-101 to target CtBP2 [99]. Circulating tumor cells (CTC) derived from the primary cancer initiate distant metastasis by entering and traversing the bloodstream. MDSCs have potential to direct interact with CTCs to form cell-cluster to promote metastasis [100]. MDSCs accumulated in the PanIN lesions in the DMBA-induced and genetically defined pancreatic cancerogenesis murine model [45]. With progression of pancreatic cancerogenesis, the proportions of MDSCs in total inflammatory cells in pancreatic lesions increased from 5.24% in normal pancreatic tissue, 9.25% in low grade PanIN, 15.25% in high grade PanIN to 22.34% in invasive pancreatic cancer [10]. In addition, increasing MDSCs in peripheral blood of pancreatic cancer patient was associated with increased risk of death, and it was an independent prognostic factor for survival [101].

In Table 2, we systematically presented the advances of the roles and mechanism of these stromal cells to regulate the malignant behaviors of pancreatic cancer in eight tumor-supporting aspects in detail during the last several years.

**Chemotherapy and tumor microenvironment**

Chemotherapy is one of the main modalities for many advanced solid malignancies. However, most of the malignancies showed resistance to chemotherapy. The
Table 2 Roles and mechanisms of the stromal cells in TME of pancreatic cancer

| Maintenance of PCSCs                                                                 | Modeling of ECM                                                                 | Proliferation and survival                                                                 | Migration                                                                 |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| **PSCs**                                                                           |                                                                                  |                                                                                          |                                                                          |
| 1. PSCs secreted-IL-6 stimulates STAT3 to enhance colony formation and progression of PanIN [102] | 1. Hypoxic PSCs exhibit highly organized parallel patterned matrix fibers to promote cancer cell motility by inducing directional migration via PLOD2 [106] | 1. PSCs induce cancer cell proliferation via galectin-1 [111] | 1. PSCs promote the migration of cancer cells via EMT process [116] |
| 2. PSCs enhance the CSCs phenotype of cancer cells by TGF-β [103]                   | 2. PSC-derived collagen I induces haptotaxis and haptotaxis of cancer cells by activating FAK signaling via binding to integrin α2β1 [107] | 2. PSCs improve the survival of cancer cell by supporting the metabolism through autophagic alanine secretion [112] | 2. PSCs promote the migration and invasion of cancer cells via Stromal Cell-Derived Factor 1/CXCR4 Axis [117] |
| 3. PSCs promote sphere formation by paracrine Nodal/Activin signaling [104]         | 3. PSCs promote invasion of cancer cells by secretion of MMP3 [108]              | 3. PSCs promote the proliferation of cancer cells via β1-integrin [113] | 3. PSCs can stimulate the proliferation, migration and chemokine (C-X-C motif) ligands 1 and 2 in pancreatic cancer cells by secreting exosomes [118] |
| 4. PSCs enhance the spheroid-forming of cancer cells and induces the expression of CSC related genes ABCG2, Nestin and LIN28 [105] | 4. TGF-β inhibits the secretion of lumican in PSCs, which could enhance PSCs adhesion and mobility [109] | 4. PSCs promote the proliferation of cancer cells by secreting kindlin-2 [114] |                                                                                      |
| 5. PSCs modulate 3D collagen alignment to promote the migration of cancer cells [110] | 5. PSCs secrete components of the ECM and change the structure of the ECM via MMPs and β1-integrin [121] | 5. Autophagic PSCs produce ECM molecules and IL6 to promote the proliferation and invasion of cancer cells [115] |                                                                                      |
| **CAFs**                                                                           |                                                                                  |                                                                                          |                                                                          |
| 1. Pancreatic cancer cells-induced expression of miR-21 in CAF promotes the clonogenicity and pancreatosphere formation [119, 120] | 1. FAP expressing fibroblasts inactivate retinoblastoma (Rb) protein in pancreatic cancer cells to promote the proliferation [124] | 1. FAP expressing fibroblasts inactivate retinoblastoma (Rb) protein in pancreatic cancer cells to promote the proliferation [124] | 1. CAFs stimulate the migration of PDAC cells through paracrine KFGF/KGFR signaling [128] |
|                                                                                  | 2. Pancreatic cancer cell induced-SOCS1 gene methylation in CAF activates STAT3 and IGF-1 expression to support growth of pancreatic cancer [125] | 2. Pancreatic cancer cell induced-SOCS1 gene methylation in CAF activates STAT3 and IGF-1 expression to support growth of pancreatic cancer [125] | 2. CAFs promote migration of pancreatic cancer cells by secreting extracellular vesicles, ANXA6/LRP1/TSP1 [129] |
|                                                                                  | 3. CAF-secreted SPARC maintain the vascular basement membrane to inhibit the metastasis of pancreatic cancer cells [123] | 3. CAF-derived CXCL12 promotes proliferation of cancer cells by binding CXCR4 [126] | 3. CAFs promote the migration and BMT of pancreatic cancer cells via IL-6 [130] |
|                                                                                  | 4. Gemcitabine treatment can increase release the exosome of CAF to promote proliferation of cancer cells through Snail [127] | 4. Gemcitabine treatment can increase release the exosome of CAF to promote proliferation of cancer cells through Snail [127] | 4. Pancreatic cancer cell-induced low expression of CD146 in CAF promoted migration and invasion of cancer cells [131] |
|                                                                                  | 5. CAFs can secrete components of the ECM and change the structure of the ECM via MMPs and β1-integrin [121] |                                                                                          |                                                                          |
|                                                                                  | 6. FAP expressing fibroblasts remodel the ECM to enhance directionality and velocity of pancreatic cancer cells by βetal-integrin/FAK/FAK signal pathway [122] |                                                                                          |                                                                          |
|                                                                                  | 7. CAF-secreted SPARC maintain the vascular basement membrane to inhibit the metastasis of pancreatic cancer cells [123] |                                                                                          |                                                                          |
|                                                                                  | 8. CAFs can secrete components of the ECM and change the structure of the ECM via MMPs and β1-integrin [121] |                                                                                          |                                                                          |
|                                                                                  | 9. FAP expressing fibroblasts remodel the ECM to enhance directionality and velocity of pancreatic cancer cells by βetal-integrin/FAK signal pathway [122] |                                                                                          |                                                                          |
|                                                                                  |                                                                                          |                                                                                          |                                                                          |
| **TAMs**                                                                           |                                                                                  |                                                                                          |                                                                          |
| 1. Pancreatic cancer potentially recruits pro-tumoral TAMs by GM-CSF and then TAMs maintain the PCSCs by IL-6/STAT3 signaling pathway [132, 133] | 1. Cancer cell derived-CCL2 induced by HIF-1 recruits TAMs to activate PSC to remodel the ECM [134] | 1. TAMs induced-upregulation of CDA improves the survival of cancer cells when treated by gemcitabine [137] | 1. TAMs secrete gliad-derived neurotrophic factor, inducing phosphorylation of RET and downstream activation of extracellular signal-regulated kinases (ERK) to promote migration of cancer cells [139] |
|                                                                                  | 2. TAMs secrete granulin to activate hepatic stellate cells, resulting in a fibrotic environment to promote liver metastasis of pancreatic cancer [135] | 2. Pancreatic cancer cells can secrete lectin Reg3 beta to promote M2 through STAT3 signal pathway and then M2 can inhibit apoptosis and prolong the viability of cancer cells [138] | 2. Soluble factors from cancer cells trigger scavenger receptor A on TAMs to promote migration of cancer cells [140] |
|                                                                                  | 3. The interactions of TAMs and PSCs contribute the fibrogenesis during pancreatic cancerogenesis [136] | 3. Pancreatic cancer cell induced low expression of CD146 in CAF promoted migration and invasion of cancer cells [131] | 3. Cancer cell over expressed heparanase induce procancerous phenotype of macrophage to promote migration of cancer cells via IL6/STAT3 signal pathway [141] |
|                                                                                  |                                                                                          |                                                                                          |                                                                          |
| **MDSCs**                                                                          |                                                                                  |                                                                                          |                                                                          |
| 1. Pancreatic cancer can induce MDSCs by STAT3 signal pathway and MDSCs increase the ALDH(+)PCSCs [142] | 1. Pancreatic cancer cells can induce MDSCs that promote tumor cell survival and accumulation [143] |                                                                                          |                                                                          |
|                                                                                  |                                                                                          |                                                                                          |                                                                          |
Table 2 continued

| EMT | Angiogenesis | Immunosuppression |
|-----|--------------|-------------------|
| **PSCs** | 1. PSCs decrease the expression of E-cadherin and ZO-1, increase the expression of β-catenin and vimentin in pancreatic cancer cells [116, 144]  
2. IL-6 from PSCs promote EMT in PDAC cells via Stat3/Nrf2 pathway [145] | 1. PSCs accompany cancer cells to metastatic sites, stimulate angiogenesis, and are able to intravasate/extravasate to and from blood vessels [146]  
2. Heptocyte growth factor (HGF)/c-Met pathway plays a role in PSC-induced tube formation of endothelial cells formation of human microvascular endothelial cells [147]  
3. PSCs express both pro- and anti-angiogenic factors to maintain the balance of angiogenesis [148] | 1. PSCs induce apoptosis and anergy of T cells via galectin-1 [149, 150]  
2. PSCs induce MDSCs via IL-6/JAK/STAT3 signaling axis [151, 152]  
3. PSCs can sequester CD8+ T cells by interaction between CXCL12 and CXCR4 [153]  
4. PSCs activate mast cells to produce IL13 and tryptase, stimulating proliferation of both cancer cells and PSCs [154] |
| **CAFs** | 1. CAF-driven CXCL12-CXCR4 signal promotes pancreatic cancer cell EMT and invasion by activating the P38 pathway [155]  
2. CAFs promote EMT of pancreatic cancer cells via IL-6/PI-3 signal pathway [156] | 1. CAFs potentially induce angiogenesis by CXCL12/CXCR4 axis and SPARC [157] | 1. CAFs induce immunosuppressive environment to dampen the effects of antibodies against CTLA-4 and PD-L1 by CXCL12 [12]  
2. CAFs weaken the function and survival of T cells by arginase II [158]  
3. CAFs induce apoptosis of T cells by galectin-1 [159]  
4. CAFs can induce M2 by secreting M-CSF to promote the pancreatic tumor cell growth, migration, and invasion [160] |
| **TAMs** | 1. M2-polarized TAMs promote EMT in pancreatic cancer cells, partially via TLR4/IL-10 signaling pathway [161]  
2. Both M1 and M2-polarized TAM decrease expression of E-cadherin and increase expression of vimentin [162] | 1. TAMs potentially induce angiogenesis by secreting VEGF to promote metastasis of pancreatic cancer [163] | 1. Blockage of CSFR reprograms TAMs to an antigen-presenting phenotype and improves antitumor T cell responses [164]  
2. TAMs potentially induce Treg to promote metastasis of pancreatic cancer [163]  
3. Radiation induced M-CSF in cancer cells recruits TAMs to construct a immunosuppressive environment to hamper antitumor response [165]  
4. Ly6C(low)F4/80(+) macrophages outside of the tumor microenvironment regulate infiltration of T cells into tumor tissue and establish a site of immune privilege [166] |
| **MDSCs** | 1. TAMs potentially induce angiogenesis by secreting VEGF to promote metastasis of pancreatic cancer [163] | 1. The MDSCs in pretumoral and pancreatic cancer tissue have high arginase activity and suppress T-cell responses [167]  
2. Pancreatic cancer induces bone marrow mobilization of MDSCs to promote tumor growth by suppressing CD8(+) T cells [168]  
3. PAUF enhance the immunosuppressive function of MDSCs via the TLR4-mediated signaling pathway [169]  
4. Pancreatic cancer dampens SHIP-1 to expand MDSCs and enhance the immunosuppressive functions [170]  
5. Depletion of Gr-MDSC, can unmask an endogenous T cell response, disclosing an unexpected latent immunity against pancreatic cancer [143] |
mechanisms of the resistance largely remain unknown. During the last several decades, the overwhelming attentions have been focused on cancer cells. However, the possible roles of tumor microenvironment in regulation the efficacy of chemotherapy have been largely neglected. On one hand, chemotherapy can direct kill or damage cancer cells, on the other hand, the chemotherapeutic drugs can also remodel the TME. For some tumors, chemotherapy could lead to immunogenic death of cancer cells and then triggered the anti-tumor immunities by activation of T cells, NK cells or macrophages. However, in contrast, chemotherapy has been also reported to remodel tumor microenvironment which promotes tumor regrowth and drug resistance. Herein, we summarized the pro-tumoral effects and anti-tumoral remodeling effects of different chemotherapeutic drugs on TME (Additional file 1: Table S2).

Conventional cytotoxic chemotherapy
After treatment with these cytotoxic drugs, the damage of the tumor tissue could be repaired to a tumor-promoting environment, which may result in promotion of tumor growth and limitation of anti-neoplastic efficacy in some tumors. After paclitaxel and doxorubicin treatment in PyMT-MMTV mammary carcinoma, increased recruitment of TAMs was found to be mediated by increased CSF-1, CCL2 and CXCL2 [52, 171]. In murine Panc02 pancreatic cancer model, gemcitabine could induce Th2 cytokines from cancer cells to promote M2 polarized TAMs [10]. In a k-ras mutated murine pancreatic cancer model, gemcitabine induced recruitment of immature myeloid cells by GM-CSF secreted from damaged cancer cells which dampened the chemotherapeutic effects [172]. In vitro study, cisplatin and carboplatin increased the expression of IL-6 in 10 gynecologic malignant cancer cell lines to induce M2 polarized TAMs [18]. TAMs can limit the effects of chemotherapy or radiotherapy by various mechanisms, such as inhibition of cytotoxic T cells, activation of Th17 cells by inflammasome-IL1β, secreting of cathepsin, protection of cancer stem cells and alter vascular permeability to inhibit intratumoral drug concentration [172, 173]. Gemcitabine and 5-FU could also trigger cathepsin B release in MDSCs to activate the Nlrp3 inflammasome and promote tumor growth [172].

In contrary, some chemotherapeutic agents could also foster anti-tumor immunities. Doxorubicin could cause ICD in immunogenic tumor models to activate macrophages and dendritic cells to promote T cell response [174]. Doxorubicin also stimulated cancer cells to release ATP, which could recruit myeloid cells and induce differentiation into antigen presenting cells, finally resulting in effective antitumor immunities [175]. After cyclophosphamide treatment, leukemic cells released CCL4, CXCL8 and VEGF to recruit and active monocytes and enhance their phagocytic activity [176]. In murine EL4 lymphoma model, gemcitabine and 5-fluorouracil (5FU) were selectively cytotoxic on MDSCs and the elimination of MDSCs increased the toxicity of CD8(+) cells [177]. Docetaxel could deplete M2 polarized TAMs and activate M1 in 4T1-Neu mammary tumor implants [178]. Trabectedin inhibited the growth of murine fibrosarcomas partially by depletion of TAMs [179].

Targeted therapies
Due to the discoveries of the molecular mechanisms of some malignancies, targeted therapies have been available to treat some tumors. Imatinib was primarily designed to treat Philadelphia chromosome positive chronic myeloid leukemia, and later it showed dramatic effects on gastrointestinal stromal tumors (GIST). In a murine GIST model, imatinib caused reduction of TAMs through CSF1R-CSF1 inhibition, however, converted TAMs to be M2 polarized type through C/EBPβ [180]. Sorafenib is a multi kinase inhibitor, including VEGFR2, and it showed active roles to treat hepatocellular carcinoma (HCC). In HCC xenograft murine model, sorafenib induced infiltration of TAMs via CXCL12, and depletion of TAMs potentiated the effects of sorafenib on angiogenesis, growth and metastasis of the tumor [181]. However, in another murine model of HCC, sorafenib was found to induce M1 polarized TAMs and to promote their stimulatory activities on NK cells [182]. Blockade of kit also showed abilities to inhibit the expansion of MDSCs and restore the immunity of T cells against tumors [183]. Antiangiogenic therapies based on inhibition of VEGF pathway could induce transient responses of tumors, however destruction of the angiogenesis created a strongly hypoxic microenvironment, which could recruit and activate MDSCs and TAMs and then they produce varieties of proangiogenic factors to stimulate angiogenesis [184]. In preclinical study, depletion of TAMs, either by clodronate-loaded liposomes or CSF-1R inhibition, increased the antitumor effects of VEGF-targeted therapies and as well combination antiangiopoietin-2 with low-dose metronomic chemotherapy successfully inhibited the repopulation of myeloid cells and achieved synergic effects [185].

Antibody based chemotherapy
Monoantibody based target therapies have shown promising effects for some kind of tumors. TAMs express Fc receptors that bind the Fc fragment of antibodies, engaging in Ab-dependent cellular cytotoxicity/phagocytosis (ADCC/ADCP). Trastuzumab, a mAb against the human epidermal growth factor receptor-2 (HER2), on one hand, directly inhibited HER2 signal pathway, on
the other hand, induced ADCC and ADCP and primed 
CD8(+) T cell responses in breast cancer [186]. TAMs 
also enhance B cell lymphoma elimination in response to 
rituximab (a moAb against CD20) through FcgR-depend-
ent ADCP and high infiltrations of TAMs were correlated 
with a better prognosis in rituximab treated patients. 

Immune checkpoints play vital roles to regulate the func-
tions of T cells in tumor tissue. Molecules involved in 
checkpoint regulation include CTLA-4 and PDL1/PDL2 
and TAMs express these immune checkpoint molecules. 
Recent evidence suggests that anti-CTLA-4 antibodies 
act via TAMs [187]. In murine models, depletion of Treg 
cells by macrophage-mediated ADCC was an essential 
component of the effects of anti-CTLA-4 [188]. How-
ever, it have been also reported that cetuximab, a moAb 
avgainst EGFR was shown to enhance the immunosup-
pressive, proangiogenic, and protumoral functions of 
TAMs in both in experimental tumor models and human 
cancers [189].

Taken together, the above studies showed the dual 
roles of chemotherapeutic drugs in regulating the tumor 
microenvironment which could significantly affect the 
efficacy of the treatments. The type of drugs, the sensitiv-
ities to the drugs of cancer cells, the immunogenic nature 
of cancer cells, the context of primary tumor microenvi-
ronment and the dynamic period after treatment should 
be considered to further delineate these interactions.

**Targeting tumor microenvironment of pancreatic cancer**

The growing importance of the stromal cells in regulation of 
almost every aspect of tumor progression leads to the 
option of therapeutic applications of targeting these cells. 
These stromal cell-targeting therapies include inhibition of 
expansion, blockade of recruitment, inhibition of acti-
vation, induction of differentiation or repolarization to 
a tumor-suppression phenotype, and even just complete 
depletion of these cells (Additional file 1: Table S3).

**MDSCs and TAMs**

The GM-CSF, G-CSF and CSF1 are key factors to pro-
mote proliferation and mobilize MDSCs and monocytes 
from bone marrow. Neutralizing antibodies to GM-CSF, 
G-CSF and CSF-1 have shown abilities to inhibit tumor 
growth in mice, including pancreatic cancer, colon can-
cer and lung cancer, by inhibition of proliferations of 
MDSCs and TAMs [52, 80, 190, 191]. Antibody to IL-6R 
[192], enzyme inhibitors, such as amino-bisphosphonate 
[193], PDE5 inhibitors [194], could inhibit proliferation of 
MDSCs to reduce the progression of breast cancer, 
colon cancer, fibrosarcoma in mice. Antibody or deple-
tion of CCL2 blocked the recruitment of MDSCs and 
TAMs in tumor microenvironment and showed effects 
to inhibit pulmonary metastasis of murine mammary 
cancer [195]. As well, antagonists of CXCR2 and CXCR4 
 altered recruitment of MDSC to the tumor to inhibit 
metastasis of murine breast cancer [196]. Depletion of 
pan-TAMs by liposome-clodronate also showed abilities 
to inhibit tumor growth in various murine tumor mod-
els (e.g., teratocarcinoma, lung cancer, and melanoma) 
and human xenograft tumor models (e.g., cervical cancer, 
head and neck cancers) [46]. However, the obvious limi-
tation of such treatment is the lack of specificity in deple-
tion of different types of TAMs. In a murine squamous 
cell carcinogenesis model, repolarization of TAMs was 
more effective than blocking recruitment or depletion of 
TAMs, since macrophages are necessary for recruitment 
and activation of T cells under some circumstances [197].
Th2 type cytokines and COX-2 are main factors to induce 
MDSC and M2 polarized TAMs. Anti-IL-10 in addition 
with an inflammatory agent like CpG results in the transi-
tion of TAMs from M2 to M1 phenotype, resulted in 
tumor inhibitions. Aspirin and Celebrex, COX-2 inhibi-
tors, showed ability to inhibit MDSCs and M2 to pre-
vent pancreatic cancerogenesis and improve the effects 
of gemcitabine [10]. Th1 type cytokines are main induc-
ers of M1 polarized TAMs. IL-12 treatment could re-
program TAMs from M2 to M1 to increase anti-tumor 
response and tumor regression in a murine lung cancer 
model [198]. Since macrophages can be activated by Fc 
receptor of immunoglobulin, monoclonal antibody to 
HER2, CD20 and CD47 have showed to activate TAMs 
to enhance antitumor activities in murine breast cancer or non-hodgkin's lymphoma [199, 200]. Increase of PD1 
expression in TAMs and MDSCs has been found, anti-
PD1 antibody also showed to activate TAMs and MDSCs 
in murine pancreatic cancer model [201]. CD40 agonist 
showed significant roles to activate the tumor-suppres-
sion effects of TAMs to improve the efficacy of gemcit-
abine in both murine pancreatic cancer model and early 
clinical trials [202]. All-trans retinoic acid (ATRA) and 
vitamin D could induce MDSC to differentiate into oste-
oclasts, and dendritic cells which reduce the immuno-
suppression [203]. Considering the ability of intratumoral 
infiltration of TAMs, TAMs also have been attempted 
to use as vehicles of drug delivery or other therapeutic 
interventions. Genetic modified TAMs expressing IFN-γ 
could induce antitumor and anti-angiogenic effects in 
murine tumor models [204]. TAM delivery of oncolytic 
virus showed to limit tumor re-growth following chem-
otherapy in a human prostate cancer xenograft model 
[205].

The strategies to target macrophages have shown 
promising effects, however the question remains which 
of these methods are more efficacious when combined 
with cytotoxic, targeted or immune checkpoint blockade
therapy. Considering the potential anti-tumor effects of macrophages, reprogramming could be a better option than pan-macrophages inhibition, depletion or blockade of recruitment.

**PSCs and CAFs**

According to the roles of CAFs and PSCs in pancreatic cancer, one would assume that CAFs and PSCs targeting may serve as powerful weapons to fight against pancreatic cancer and to improve therapeutic effects, however the up to date results are conflicting and more complicated than we can imagine. Sonic hedgehog (shh) pathway inhibitor IPI-926 was applied to deplete desmoplastic stroma and CAFs in pancreatic cancer, and the finding resulted in increased vascularization and more effective drug delivery of gemcitabine, with improved overall survival in KPC mouse model [206]. Clinical trials of anti-angiogenesis therapies did not show benefit in pancreatic cancer, when combined with gemcitabine [207, 208]. This finding could explain why these anti-angiogenesis therapies failed to improve the effects of gemcitabine, as these approaches would potentially lead to decrease intratumoral concentration of chemotherapeutic agents. However, when combined with the FOLFIRINOX regimen, IPI-926 led to a shorter median survival in pancreatic cancer patients [209]. The MMPs are the enzymes that are most responsible for degrading ECM components which potentially enhance the effects of gemcitabine. However, high expressions of MMP2, MMP7 and MMP11 in pancreatic cancer were found to be associated with a poor prognosis [210]. The clinical trials of MMP inhibitors, either alone or in combination with gemcitabine have not shown positive results [211]. Moreover, recent study based on PKT spontaneous pancreatic cancer mice model, depletion of desmoplastic stroma might promote the ability of cancer cells to invade the surrounding tissue and metastasize [212–214]. In accordance with results from PKT mice, small numbers of α-SMA positive CAFs in human pancreatic cancer tissue predicted shorter survival [212].

Vitamin D can induce quiescence of CAFs and pSCs. Calcipotriol, a analogue of vitamin D, was administered with gemcitabine into KPC mice, resulting in obvious reduction of tumor in most of the mice, with a dramatic increase of intratumoral concentration of gemcitabine by 500% [215]. ATRA can also convert activated PSCs to quiescent PSCs to slow tumor progression and migration in mice pancreatic cancer model [216]. It is also believed that dense stroma tissue will increase interstitial fluid pressure (IFP) and then limits the delivery of chemotherapeutic drugs into cancer tissue. After treatment by PEGPH20, a hyaluronan-degrading enzyme, the IFP was decreased and functional perfusion of collapsed vascular structures was restored. Better survival was observed in pancreatic cancer bearing mice with a combination of PEPH20 and gemcitabine [217, 218]. Phase I clinical trial of PEGPH 20 showed no obvious toxicity and phase II clinical trial are planned [219]. Nab-paclitaxel is a combination of albumin and paclitaxel which has shown to improve the effects of gemcitabine. Albumin enables paclitaxel to transcytosis across endothelial cells through albumin receptors and then SPARC in tumor stroma has high affinity to albumin, which allows paclitaxel accumulation and then paclitaxel can induce stromal collapse, resulting greater efficacy of gemcitabine delivery and concentration in the tumor. In a current phase III clinical trial, the combination of nab-paclitaxel and gemcitabine have shown inspiring results [23]. In addition to the aspects of ECM, CAFs can also sequester T cells by expression of CXCL12, and AMD3100, an inhibitor of CXCR4, could block the effects of CXCL12 of CAFs and enhanced the effects of antagonist of PDL1 in KPC mice [220].

Taken together, the above studies indicated the complicated effects of the desmoplastic tumor stroma targeting therapies. Most of the studies showed that depletion of desmoplasia, inactivation of PSCs and CAFs could improve the effects of gemcitabine in mice model, however the clinical trials did not get equal satisfactory results as in mice models. And even, recent studies supported the idea that the desmoplastic stroma might form a barrier that reduced the invasion and metastasis of cancer cells. Hence, the roles of desmoplastic stroma seem to be context-dependent during different stages of the tumor and under different treatment. Since the PSCs and fibroblasts have vital physiological roles, induction of quiescence of PSCs and CAFs, might be a better promising approach than complete ablation of desmoplastic stroma for future development of therapies targeting tumor desmoplasia of pancreatic cancer.

**Conclusion**

Pancreatic cancer will be the second leading cancer death in USA in 2030. Although tremendous efforts have been put on the study of pancreatic cancer cells, the improvements of survival have been minimally limited. The complicated network consisting of PSCs, CAFs, TAMs, MDSCs and cancer cells play crucial roles in pancreatic cancerogenesis, tumor progression, metastasis and drug responses. In addition to direct toxicities to cancer cells, chemotherapy can also remodel the TME, affecting the efficacy, or even contributing to drug resistance (Fig. 1). New treatments, targeting the tumor microenvironment, are highly warranted, however there are still some aspects need further explorations: (1) since Th2 cytokines are main cytokines to activate or polarize PSCs, CAFs,
TAMs and MDSCs, it is of great importance to uncover why pancreatic cancer cells express high level of the Th2 cytokines; (2) there are many crosstalk between these five cell populations, which could dwarf the effects of any single target therapy, so combinational treatment may provide better results; (3) since of the diversities of the functions of PSCs, CAFs, TAMs and MDSCs, which could potentially contribute to anti-tumor effects, the regulations of the functions of these cells could be more effective than that of complete depletion of all of these cells; (4) since these stromal cells can seldom kill or damage cancer cells directly, the combinations of stroma cell-targeting treatments with direct cancer cell-targeting treatments could warrant better results; (5) among these five cell populations, M2 polarized TAMs express exclusive surface markers (e.g., CD206, CD163) which are seldom expressed on other immune cells or any other tissues, and there are also abundant infiltration of M2 polarized TAM in pancreatic cancer tissue, in contrast, these cells are seldom found in the peripheral blood or any other part of normal tissue, so these M2 exclusive surface markers could be applied as targets for directional intratumoral drug delivery.

**Additional file**

**Additional file 1: Table S1.** The chronological list of landmark events of chemotherapy in pancreatic cancer from 2000. **Table S2.** The pro-tumoral and anti-tumoral remodeling effects of chemotherapy on TME. **Table S3.** Tumor microenvironment targeting therapies of pancreatic cancer.

**Fig. 1** The landscape of tumor microenvironment (TME) of pancreatic cancer: (1) the PSCs, CAFs, MDSCs and TAMs promote the malignant biological behaviors of pancreatic cancer through eight aspects; (2) the phenotypes and functions of PSCs, CAFs, MDSCs and TAMs in TME of pancreatic cancer are dynamically changed and they can regulate each other; (3) bone marrow is the most importance origination for TAMs and MDSCs, and as well the bone marrow contributes to the PSCs and CAFs; (4) the cancer cells, including bulk cells and cancer stem cells (CSCs) in tumor tissue, are the main triggers to induce the architecture of TME, after chemotherapy, the damaged cancer cells, apoptotic cancer cells or immunogenic death of cancer cells can secrete varieties of signals to act on the stroma cells in TEM or to expand, recruit and activate bone marrow derived cells to remodel the TME, eventually affecting the efficacy of treatments or even leading to drug resistance.
Abbreviations
ATRA: all-trans retinoic acid; ARG1: arginase1; bFGF: basic fibroblast growth factor; CAFs: cancer associated fibroblasts; CSF-1: colony stimulating factor-1; COX-2: cyclooxygenase-2; CSCs: cancer stem cells; CTGs: circulating tumor cells; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; CXCCL: c-c motif ligand; CXCR: receptor of c-c motif ligand; DAMPs: damage associated molecular patterns; DMBA: dimethylbenzanthracene; ECM: extracellular matrix; EMT: epithelial mesenchymal transition; FAP: fibroblast activation protein; GCC: gastrointestinal stromal tumors; GM/M-CSF: granulocyte macrophage/macrophage colony stimulating factor; GLP-1: glucagonlike peptide 1; HCC: hepatocellular carcinoma; HMGBl: high-mobility group box 1 protein; KID: immunogenic cell death; iMCs: immature myeloid cells; IFN-γ: interferon-γ; MDSCs: myeloid derived suppressor cells; MMPs: metal matrix proteases; PanIN: pancreatic intraductal neoplasia; PDAC: pancreatic ductal adenocarcinoma; PD-1: programmed death 1; PGE2: prostaglandin E2; PSCs: pancreatic stellate cells; STAT: signal transducer and activator of transcription; PCSCs: pancreatic cancer stem cells; PDGF: platelet-derived growth factor; TME: tumor microenvironment; Treg: regulatory T cells; TAMs: tumor associated macrophages; Th2: T helper 2; TGFβ: transforming growth factor beta; TNFα: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor.

Authors' contributions
QFL, YPZ and QL designed the structure of this paper. QFL wrote the manuscript. YPZ and QL revised the manuscript. All authors agreed to send this manuscript to Cancer Cell International for publication. All authors read and approved the final manuscript.

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Competing interests
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