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SYSTEMATIC REVIEW

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Prognostic biomarkers related to tumoral microenvironment in pancreatic ductal adenocarcinoma: a systematic review

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Abstract

Over the past decades, pancreatic ductal adenocarcinoma (PDAC) has been coming into view due to increased mortality, the 5-year survival rate being the lowest of all cancers (around 6%). In PDAC, microenvironmental components possess prognostic relevance. The aim of this article is to perform a review of studies evaluating the composition of the tumor microenvironment to identify tumor microenvironment-related prognostic biomarkers in patients with PDAC. A literature search has been performed in three major databases *PubMed®*, *Embase®*, *Web of Science®* using the search terms: pancreatic adenocarcinoma in combination with one of the following: alpha-smooth muscle actin (α-SMA), collagen I, cluster of differentiation (CD)31, CD105, CD3–CD4–CD8, CD68 and CD206. Total number of articles identified through database searching was 1185. After title and abstract review, we have selected 92 articles in which the markers sought were studied. Tumor microenvironment-related biomarkers appear to also possess role in monitoring the response to treatment. Thus, CD105 angiogenetic immunomarker, stromal immunomarkers such as α-SMA and collagen I, immune cells markers represented by CD4/CD8 ratio, CD206 and CD68 were correlated with negative prognosis, while CD3+, CD8+ immune cells markers and CD31 angiogenetic immunomarker proved to be correlated with good prognosis. Furthermore, most studies were performed on resected specimens and culture cells, while only a few studies used specimens obtained through endoscopic ultrasound-guided fine-needle biopsy (EUS–FNB). To increase the therapeutic response and reduce toxicity, prognostic targets should be determined on a large scale, not only based on resected specimens. EUS–FNB represents a feasible method to provide sufficient tissue for diagnosis and additional immunohistochemistry analysis.

Keywords: pancreatic ductal adenocarcinoma, endoscopic ultrasound-guided fine-needle biopsy, collagen I, alpha-smooth muscle actin, CD31.

Introduction

Over the past decades, pancreatic ductal adenocarcinoma (PDAC) has been coming into view due to increased mortality, the 5-year survival rate being the lowest of all cancers (around 6%), according to *American Cancer Society* (ACS) [1]. Thus, the poor prognosis can be attributed to rapid progression, lack of specific symptoms which leads to a delay in diagnosis, early metastasis and resistance to standard therapy [2]. In addition, PDAC ranks first in the projected top 3 deadliest cancers in 2030 along with lung and liver tumors.

Therefore, to improve survival in PDAC, it is essential to identify and understand prognostic factors that will help us to select patients responsive to treatment, avoiding the cases where patients experience only increased toxicity to chemotherapy regimens. Furthermore, PDAC aggressiveness and resistance to treatment is attributed to abundant tumor desmoplasia, a reaction in which acellular extracellular matrix (ECM) infiltrates the cellular stromal component. Stroma consisting of ECM and cellular stromal component represents more than 50% of the tumor volume and depleting it seems to have a promising therapeutic role [3]. Interactions between stroma or properly termed tumor environment and tumor cells seem to have a central role in therapeutic resistance. In another train of thoughts, it is of paramount importance to understand that the tumor microenvironment is a complex entity made of pancreatic stellate cells (PSCs), immune cells, blood vessels, ECM, proteins such as growth factors or cytokines and their interactions have a prognostic relevance according to former results [4].

Aim

The aim of this paper was to perform a review of studies evaluating the composition of the tumor microenvironment data related to angiogenesis, stromal activation or desmoplasia and immune cells infiltrations, by analyzing publications visible in the most commonly referred medical databases, *i.e.*, *PubMed®*, *Embase®* and *Web of Science®*.

Materials and Methods

Several markers related to tumor environment have been selected for analysis. Angiogenesis immunomarkers selected

for research were cluster of differentiation (CD)31 and CD105. Desmoplasia-related biomarkers were alpha-smooth muscle actin (α-SMA) and collagen I. CD3 (T-lymphocytes), CD4 (T-helper lymphocytes), CD8 (cytotoxic T-lymphocytes), CD68 (pan-macrophage marker), and CD206 (M2 macrophage marker) have been selected as markers related to immune cells infiltration. A literature search has been performed in three major databases *PubMed®*, *Embase®*, *Web of Science®* using the search terms: pancreatic adenocarcinoma in combination with one of the following: α-SMA, collagen I, CD31, CD105, CD3–CD4–CD8, CD68 and CD206. The total number of articles identified through database searching was of 1185. After title and abstract review, we have selected 92 articles in which the markers sought were studied, and these were further reviewed in full text (Figure 1). The studies corresponded to each marker were carefully analyzed.

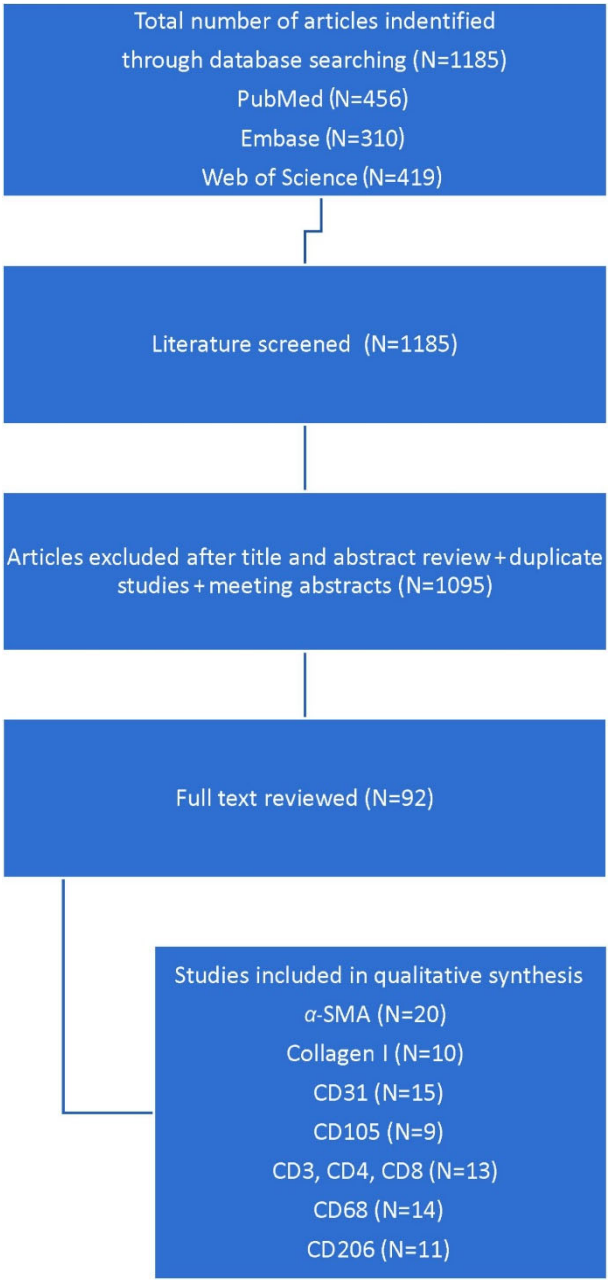

Figure 1 – ***Flow diagram of study selection. α-SMA: Alpha-smooth muscle actin; CD: Cluster of differentiation.***

Stromal activation biomarkers

α-SMA

The literature search identified 20 articles evaluating the role of α-SMA in PDAC.

It appears that α-SMA is expressed on the surface of cancer-associated fibroblasts (CAFs), a component of desmoplastic stroma in PDAC. Drug penetration is inhibited by desmoplasia described as abundant stromal response [5]. CAFs seem to be the main producer of ECM and PSCs the main source of CAFs [6].

Low density α-SMA CAFs on surgical specimens has been observed in a retrospective study of 65 patients after the Gemcitabine + nanoparticle albumin-bound (Nab)-Paclitaxel regimen, compared with untreated or Gemcitabine plus S-1 groups [7]. These results are in line with other studies in which high α-SMA levels in tumoral stroma has been associated with worse outcome [8–10].

The stromal activity index (the ratio of α-SMA and collagen density) represents a fine indicator of fibrotic activity and a prognostic tool. His role was studied on 233 PDAC patients. High stromal activity index on surgical specimens was associated with poor prognosis [11]. Another study revealed that deletion of α-SMA positive CAFs in mice with PDAC negatively influenced the prognosis [12].

Intriguingly, data suggested that high expression of α-SMA cannot be equalized with a dense stroma reaction, if dense stroma is associated with improved survival. There is an assumption that other mechanisms are being involved, but not yet elucidated [13].

Decreased expression of α-SMA CAFs and collagen in the peritumoral stroma has been correlated with enhanced intratumorally drug distribution due to the addition of Pentoxifylline [14] or Metformin [15] in studies made on human PDAC xenograft models [16].

Combination of microvessel density (MVD)–CD34 and α-SMA-positive stromal cell density has been followed in 57 resected pancreatic tumors. The combination of high MVD–CD34 and low α-SMA predicted a negative prognosis regarding early recurrence and death. Moreover, the endothelial and α-SMA-positive cells superpose, especially on vascular walls, leading to low microvessel integrity, early recurrence, and metastasis [17].

In short, α-SMA has been intensely studied on surgical specimens and it was correlated with poor prognosis. Furthermore, his role has been also emphasized in human PDAC xenograft models in which treatment efficiency was associated with low immunoexpression of α-SMA.

Type I collagen

The literature search revealed 10 articles related to the prognostic value of type I collagen in PDAC patients. Even though dense ECM with his main component type I collagen looks like a fortress, where tumoral cells are not allowed to enter, collagen I fibers act as pathways to facilitate migration and guide tumoral cells in areas intensely vascularized [18, 19].

On cell cultures, it has been observed that collagen I is able to disrupt the E-cadherin adhesion complex, reducing cellular adhesion and promoting proliferation in PDAC. Type I collagen activates focal adhesion kinase (FAK), which translocate to E-cadherin adhesion complex to

dismantle it. This process is correlated with higher amounts of nuclear β-catenin and transcription factors which promote invasiveness by increasing the expression of cell cycle proteins [20].

Besides tumor migration and invasion, type I collagen in cell cultures appears to make tumoral cells resistant to chemotherapy. Thus, has been noticed that collagen I upregulates membrane type I matrix metalloproteinase (MTI–MMP) and consequently enhances the expression of MTI–MMP-dependent high mobility group A2 (HMGA2), a deoxyribonucleic acid (DNA)-binding nuclear protein with a key role in gene transcription and chromatin remodeling, thereby minimizing the effect of Gemcitabine [21, 22]. Other study in a mice model of breast cancer revealed that a selective MTI–MMP antibody showed good results in inhibiting invasiveness [23]. Therefore, targeting of MTI–MMP in a selective manner may represent an alternative to enhance the response to chemotherapy.

In addition, in the presence of cancer cells, collagen I and IV, together with fibronectin has been shown to stimulate monocytes with the aim of producing cytokines. Particularly, these ECM powerful compounds inhibit the release of tumor necrosis factor (TNF) [24].

Taking into consideration that metastatic disease represents the leading cause of death, some researchers studied the amount of collagen I in PDAC metastasis. Their conclusion was that both PDAC metastasis and primary tumor contain large quantities of collagen I [25].

Decreased expression of collagen I has been correlated with enhanced intratumorally distribution of Gemcitabine due to the addition of Mycophenolate Mofetil (MMF) and Everolimus [26]. Thereby, MMF and Everolimus prevent invasion and risk of metastasis by increasing the potency of Gemcitabine. Still, these results were obtained only *in vitro*, phase II and III studies are needed to be validated taking into consideration that the combination of immunosuppressants and cytostatic may cause surprises in terms of side effects [27].

In a word, studies made on cell cultures highlighted that type I collagen promotes invasiveness and resistance to chemotherapy, being considered along with α-SMA, a stromal marker of negative prognosis.

Angiogenesis markers

CD31 (PECAM-1)

Our literature search identified 15 articles evaluating CD31 [platelet endothelial cell adhesion molecule-1 (PECAM-1)] in PDAC.

Angiogenesis or growth of new blood vessels from pre-existing ones, plays a key role in cancer physiopathology. Any tumor larger than 3 mm in diameter needs new blood vessels to grow. Thus, it is well known for different types of tumors that the more vessels the tumor has the more aggressive it behaves. However, on particular types of cancers, such as PDAC, high vascularity is associated with better prognosis [28]. Thus, adding Bevacizumab to Gemcitabine in a phase III trial did not bring any benefit in PDAC [29].

As we are aware, due to the hypovascular pattern and peritumoral dense stroma the penetration of cytostatic is difficult. Stromal components enhance the interstitial fluid pressure and create a network which acts as a barrier to drug release. In contrast to other tumors, in PDAC fibroblasts and dense stroma inhibit angiogenesis. CD31 represents a specific immunomarker for vascularity being expressed mainly in vascular endothelial cells, according to a recent study. In a cohort of 150 patients with PDAC, it has been shown that increased expression of CD31 has been associated with remarkable better outcome. Besides, in the CD31-expressing tumors, both immune response and vascular stability related pathways were upregulated. Regarding immune response, anti-tumor immune cells, such as CD4+ T-cells, CD8+ T-cells, naïve B-cells have been noticed predominantly, whilst regulatory T-cells (Tregs) responsible for immune tolerance were observed occasionally. Better overall survival (OS) in high CD31-expressing tumor may be due to a larger number of stable vessels that acts as highways for anti-cancer immune cells [30].

It has been shown in pancreatic cancer cell lines that the expression of CD31 at the invasive front of the stroma is low due to PSCs that promote hypoxia by abnormal periostin-rich matrix deposition and by stimulating cancer cells to produce endostatin, a factor that inhibits angiogenesis [31]. Also in cell lines, it has been discovered that CD31-positive MVD may be inhibited by Xanthohumol, a prenylated flavonoid from the hop plant. Xanthohumol, in cell cultures, has an anti-angiogenetic effect by suppressing the transcription of nuclear factor-kappa B (NF-κB) and it was proposed as a novel target in the treatment of pancreatic cancer [32]. Moreover, Curcumin in combination with Gemcitabine also has proved to decrease CD31-positive MVD by inhibiting NF-κB [33]. To sum up, in a cohort of 150 pancreatic resected specimens, CD31 proved to be correlated with o good prognosis.

CD105 (endoglin)

CD105 or endoglin role in PDAC was assessed in nine studies.

Endoglin, a transmembrane glycoprotein and part of transforming growth factor-beta (TGF-β) receptor system expressed in endothelial cells promotes proliferation through pathways upregulated by hypoxia.

In a recent study, CD105 was proven to be a specific immunomarker for angiogenetic vessels, whilst CD31 was expressed also in immature or old vessels that are not involved in tumoral growth [34]. Expression of CD105 as a label of MVD was assessed in 42 pancreatic adenocarcinoma resected specimens. Tumor, node and metastasis (TNM) stage was associated with increased expression of CD105. Therefore, high CD105-positive MVD has been correlated with poor OS [35].

Other study proposed a novel strategy to assess angiogenesis and response to treatment. The usage of contrast ultrasound with targeted microbubbles [CD105, vascular endothelial growth factor (VEGF) receptor 2, VEGF-activated blood vessels] has been demonstrated to correlate with the intratumorally level of the target and with MVD. Moreover, targeted microbubbles may be used to monitor vascular effects of anti-angiogenetic therapy [36].

Endoglin has been proposed to be used as a target for novel therapies to inhibit angiogenesis and lymph angiogenesis. Additionally, CD105 may be useful as a prognostic

marker, assessing with higher accuracy MVD [37]. Moreover, it has been revealed that using dual targeting of anti-tissue factor (TF) and CD105 in positron emission tomography (PET) imaging it can help in monitoring the response to treatment and also may increase diagnostic yield [38]. In conclusion, endoglin represents an angiogenetic marker of great value in predicting response to treatment and monitoring its effectiveness, being intensely correlated with negative prognosis.

Immune cells markers

CD3 (T-lymphocytes), CD4 (T-helper lymphocytes), CD8 (cytotoxic T-lymphocytes)

Thirteen articles were found regarding role of immune cells markers in PDAC.

Tumor microenvironment contains also tumor-infiltrating lymphocytes (TILs), intensely studied due to their antitumoral role. Both CD3+ and CD8+ T-cells possess cytotoxic properties to recognize and kill cancer cells. CD4+ T-cells are in charge with CD20+ B-cells and CD8+ T-cells activation, and in turn CD4+ T-cells are regulated by cytokines to differentiate into forkhead box P3 (FoxP3)+ T-cells immunosuppression regulators. Furthermore, CD4+ and CD2+ modulate immune response by showing increased versatility, whilst Tregs, such as FoxP3+ mediate immunosuppression [39]. Therefore, cytotoxicity of natural killer (NK) cells and CD8+ T-cells (NK) represents the mechanism that underpins current immunotherapies [40].

Prognosis and progression seem to be influenced by specific TILs. Smaller tumors were associated with increased level of CD3. In contrast, CD4/CD3 ratio was related to poor outcome in 43 pancreatic resected specimens [41].

A recent meta-analysis including 4758 patients with resected pancreatic cancer concluded that high density of CD8+ and CD3+ T-lymphocytes in PDAC resected specimens corresponded with increased OS and death free survival (DFS). Additionally, at the opposite pole, FoxP3+ T-lymphocytes were correlated with worse prognosis. CD4+ T-cells did not influence the OS, the apparent explanation being on the grounds that FoxP3+ Tregs expressed also CD4 coreceptors. Thereby, distribution of CD8+ T-lymphocytes in the center of the tumor and not at the periphery showed a better outcome [42, 43]. Other data revealed that a low density of CD3, CD8 and CD68 was correlated with worst progression free survival [44]. In the postoperative settings, including 160 resected pancreatic specimens, CD3+ level was discovered to return to preoperative status within 4–6 weeks. Also, the predominance of immune promoting cells was observed in the postoperative setting, underlying the idea that tumoral resection can reverse immunosuppression [45].

Considering that immune cells may eliminate cancer cells whether a direct cell-to-cell contact has been made, it is necessary to bear in mind that fibrotic stroma in PDAC hinders immune cells to get closer to cancer cells [46]. Targeting immune cells in parallel to dense stroma may represent an approach of the utmost importance. Other studies emphasized on the prognostic role of landscaping TILs inside the tumor, as a matter of guidance in choosing personalized immune checkpoint therapy [47].

Density of CD3, CD4, CD8 T-cells was shown to be minimal in pancreatic cancer and it was distributed almost exclusively in stroma area, in contrast to melanoma where an increased number of immune infiltrates was found in the peritumoral area. Furthermore, it was discovered that metastatic PDAC contains lower immune cells than resected PDAC [48].

It is well known that programmed death-1 (PD-1) receptor interacts with his ligand (PD-L1) to suppress T-cells activity. Cell lines studies have underlined the role of PD-1–CD28 fusion protein in transducing CD4+ and CD8+ T-cell. Furthermore, this mechanism has overcome PD-1–PD-L1 axis. To complete the picture, the synergistic activity of CD4+ and CD8+ T-cells concentrations boosted antitumoral activity [49].

In 212 patients with unresectable PDAC and with ongoing chemotherapy, the circulating Tregs were sought through endoscopic ultrasound-guided fine-needle biopsy (EUS–FNB) a specimen was obtained with the aim to perform immunohistochemical analysis. Researchers have proved that low Tregs or decreased CD4/CD8 ratio after two cycles of Gemcitabine increased OS. Moreover, after cytostatic, in partial remission or stable disease the level of Tregs were significantly low [50]. Concluding, it has been proved that Tregs may predict OS in patients with unresectable PDAC and with ongoing chemotherapy [51].

In brief, using resected specimens or specimens obtained through EUS–FNB, the role of TILs regarding prognosis was assessed. On one hand, CD3+, CD8+ was associated with increased OS, on other hand increased CD4/CD8 ratio predicted worse prognosis.

CD68

Tumor-associated macrophages (TAMs) labeled by CD68 deriving from circulating monocytes are involved in the initiation, tumor growth and cells spreading. Thus, according to recent studies, TAMs turned out to have a prognostic role in many solid tumors.

Two classes of TAMs have been described. M1 macrophages (CD163, CD204, CD206) have antitumoral and proinflammatory effects, after activation by T-helper type 1 (Th1) cytokines. In contrast, M2 macrophages (CD163, CD204, CD206), named alternatively activated macrophages, are regulated by T-helper type 2 (Th2) cytokines and possess pro-tumor effects encouraging tissue remodeling and tumor proliferation [52].

A meta-analysis made on 1699 patients with resected pancreatic cancer revealed that high density CD68+ TAMs in PDAC was associated with bad outcome [53] and aggressiveness [54, 55]. Due to the differentiation of TAMs in two classes, M1 and M2 macrophages have been intensively studied to elucidate their role in prognostic prediction. Therefore, studies showed that M2–TAMs were also correlated with poor OS, regarding their role especially in invasiveness [56–58]. Given the above, M2–TAMs may be used rather as therapeutic target than a prognostic factor in future studies [59].

Another study including 70 resected pancreatic specimens revealed a strong correlation between tumor CD68+ cells and interleukin 8 (IL8) expression. Furthermore, IL8-positive CD68 TAMs seem to negatively influence the prognosis. Thus, blocking IL8 may have therapeutical implication if IL8 signaling engages both tumoral and inflammatory cells [60].

In addition, in 74 patients with PDAC or chronic pancreatitis and pancreaticoduodenectomy, CD68+ TAMs seem to accumulate peripherally. Thus, non-cancerous cells are responsible for recruitment and polarization of macrophages through chemoattractants secreted by myofibroblasts [61]. More M2–TAMs were identified in PDAC in both peripheral and central areas than in chronic pancreatitis [62].

Although CD68 TAMs have intense pro-tumoral effects [63], after treatment with Gemcitabine they become tumoricidal. This means that the quantification of CD68 TAMs before chemotherapy may be essential in choosing the most appropriate patients for treatment [64]. To conclude, CD68 TAMs is an immune cell marker of negative prognosis involved in predicting response to treatment.

CD206

CD206 represents a label among others (CD163, CD204) for M2 macrophages. M2 macrophages are located more often in large tumors and are correlated with early recurrence and metastasis. Although it was believed that tumor cells were responsible for the activation of M2–TAMs, in culture cells myofibroblasts seem to activate them. Therefore, CAFs stimulate secretion of macrophage colony-stimulating factor (M-CSF), consequently activating M2–TAMs [65]. Additionally, CAFs may induce immune suppression implying reactive oxygen species (ROS) as a modulator of M2 transformation [66].

Considering that a recent study including 77 resected pancreatic cancers specimens revealed a correlation between pyruvate kinase M2 (PKM2) and M2–TAMs polarization, co-expression of CD206 and PKM2 was studied. In was shown that CD206 and PKM2 have a negative influence on the prognosis and act synergistically. Dual target approach may be a reasonable strategy to move forward with innovative therapies [67]. Polarization of TAMs to M2 was promoted also by regenerating islet-derived protein 4 (REG4) according to other study [68]. REG family contains proteins that influence inflammatory cells in digestive organs [69]. Poorly differentiated PDAC cells have an increased expression of REG4 correlating with high serum level of REG4 in PDAC patients [70]. To resume, CD206 together with CD68 represent labels for TAMs and are correlated with poor outcome.

EUS–FNB and tumor microenvironment-related biomarkers

EUS–FNB has become lately the method of choice to procure pancreatic tissue in suspected pancreatic lesions [71]. FNB devices have unique geometries and are used preferentially in solid tumors in order not only to depict tissue architectures, but also to make a molecular or genetic characterization. Although the tissue yield for these needles has varied from 59% to 95% [72–74], a recent study made on 129 patients revealed a diagnostic accuracy of 90%.

Tumor microenvironment-related biomarkers appear to possess not only prognostic value but also role in monitoring the response to treatment. Thus, stromal markers such as α-SMA and collagen I were correlated with negative prognosis promoting resistance to chemotherapy. Regarding angiogenesis, CD31 proved to be correlated with good prognosis, although endoglin was intensely associated with negative prognosis, predicting response to treatment, and having a key role in monitoring the response to chemotherapy. As for immune cells markers, CD3+, CD8+ were associated with increased OS. In contrast, CD4/CD8 ratio predicted worse prognosis and CD206 together with CD68, labels for TAMs were correlated with poor outcome. Furthermore, most studies were performed on resected specimens and culture cells only a few studies used specimens obtained through EUS–FNB.

Further studies are needed to evaluate the feasibility of analyzing the above-mentioned biomarkers on pancreatic specimens obtained by EUS–FNB.

Conclusions

To increase the therapeutic response and reduce toxicity prognostic targets should be determined on a large scale, not only on resected specimens. Several tumor microenvironment-related biomarkers appear to possess not only prognostic value but also role in monitoring the response to treatment. Thus far, most studies were performed on resected specimens and culture cells and only a few studies used specimens obtained through EUS–FNB. As EUS–fine-needle aspiration (FNA) is the procedure of choice to diagnosis PDAC, further studies are needed to evaluate the feasibility of analyzing tumor microenvironment-related biomarkers on EUS–FNB samples.

Conflict of interests

There is no conflict of interests.

Acknowledgments

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References

[1] Andoh A, Takaya H, Saotome T, Shimada M, Hata K, Araki Y, Nakamura F, Shintani Y, Fujiyama Y, Bamba T. Cytokine regulation of chemokine (IL-8, MCP-1, and RANTES) gene expression in human pancreatic periacinar myofibroblasts. Gastroenterology, 2000, 119(1):211–219. https://doi.org/10.1053/gast.2000.8538 PMID: 10889171

[2] Bang JY, Hebert-Magee S, Navaneethan U, Hasan MK, Hawes R, Varadarajulu S. EUS-guided fine needle biopsy of pancreatic masses can yield true histology. Gut, 2018, 67(12):2081–2084. https://doi.org/10.1136/gutjnl-2017-315154 PMID: 28988195 PMCID: PMC6241607

[3] Cazacu IM, Singh BS, Saftoiu A, Bhutani MS. Recent developments in hepatopancreatobiliary EUS. Endosc Ultrasound, 2019, 8(3):146–150. https://doi.org/10.4103/eus.eus_20_19 PMID: 31031329 PMCID: PMC6590003

[4] Blando J, Sharma A, Higa MG, Zhao H, Vence L, Yadav SS, Kim J, Sepulveda AM, Sharp M, Maitra A, Wargo J, Tetzlaff M, Broaddus R, Katz MHG, Varadhachary GR, Overman M, Wang H, Yee C, Bernatchez C, Iacobuzio-Donahue C, Basu S, Allison JP, Sharma P. Comparison of immune infiltrates in melanoma and pancreatic cancer highlights VISTA as a potential target in pancreatic cancer. Proc Natl Acad Sci U S A, 2019, 116(5):1692–1697. https://doi.org/10.1073/pnas.1811067116 PMID: 30635425 PMCID: PMC6358697

[5] Bramhall SR, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JAC. A double-blind placebo-controlled, randomised study comparing Gemcitabine and Marimastat with Gemcitabine and placebo as first line therapy in patients with advanced

pancreatic cancer. Br J Cancer, 2002, 87(2):161–167. https://doi.org/10.1038/sj.bjc.6600446 PMID: 12107836 PMCID: PMC2376102

[6] Chen SJ, Lian GD, Li JJ, Zhang QB, Zeng LJ, Yang KG, Huang CM, Li YQ, Chen YT, Huang KH. Tumor-driven like macrophages induced by conditioned media from pancreatic ductal adenocarcinoma promote tumor metastasis *via* secreting IL-8. Cancer Med, 2018, 7(11):5679–5690. https://doi.org/10.1002/cam4.1824 PMID: 30311406 PMCID: PMC6246928

[7] Clark CE, Beatty GL, Vonderheide RH. Immunosurveillance of pancreatic adenocarcinoma: insights from genetically engineered mouse models of cancer. Cancer Lett, 2009, 279(1):1–7. https://doi.org/10.1016/j.canlet.2008.09.037 PMID: 19013709

[8] Condeelis J, Segall JE. Intravital imaging of cell movement in tumours. Nat Rev Cancer, 2003, 3(12):921–930. https://doi.org/10.1038/nrc1231 PMID: 14737122

[9] Delany AM. Matricellular proteins osteopontin and osteonectin/SPARC in pancreatic carcinoma. Cancer Biol Ther, 2010, 10(1):65–67. https://doi.org/10.4161/cbt.10.1.12452 PMID: 20657168 PMCID: PMC3230283

[10] Delayre T, Guilbaud T, Resseguier N, Mamessier E, Rubis M, Moutardier V, Fara R, Berdah SV, Garcia S, Birnbaum DJ. Prognostic impact of tumour-infiltrating lymphocytes and cancer-associated fibroblasts in patients with pancreatic adenocarcinoma of the body and tail undergoing resection. Br J Surg, 2020, 107(6):720–733. https://doi.org/10.1002/bjs.11434 PMID: 31960955

[11] Deng YR, Liu WB, Lian ZX, Li X, Hou X. Sorafenib inhibits macrophage-mediated epithelial–mesenchymal transition in hepatocellular carcinoma. Oncotarget, 2016, 7(25):38292–38305. https://doi.org/10.18632/oncotarget.9438 PMID: 27203677 PMCID: PMC5122390

[12] Devy L, Huang L, Naa L, Yanamandra N, Pieters H, Frans N, Chang E, Tao Q, Vanhove M, Lejeune A, van Gool R, Sexton DJ, Kuang G, Rank D, Hogan S, Pazmany C, Ma YL, Schoonbroodt S, Nixon AE, Ladner RC, Hoet R, Henderikx P, Tenhoor C, Rabbani SA, Valentino ML, Wood CR, Dransfield DT. Selective inhibition of matrix metalloproteinase-14 blocks tumor growth, invasion, and angiogenesis. Cancer Res, 2009, 69(4):1517–1526. https://doi.org/10.1158/0008-5472.CAN-08-3255 PMID: 19208838

[13] Di Caro G, Cortese N, Castino GF, Grizzi F, Gavazzi F, Ridolfi C, Capretti G, Mineri R, Todoric J, Zerbi A, Allavena P, Mantovani A, Marchesi F. Dual prognostic significance of tumour-associated macrophages in human pancreatic adenocarcinoma treated or untreated with chemotherapy. Gut, 2016, 65(10):1710–1720. https://doi.org/10.1136/gutjnl-2015-309193 PMID: 26156960

[14] Di Maggio F, Arumugam P, Delvecchio FR, Batista S, Lechertier T, Hodivala-Dilke K, Kocher HM. Pancreatic stellate cells regulate blood vessel density in the stroma of pancreatic ductal adenocarcinoma. Pancreatology, 2016, 16(6):995–1004. https://doi.org/10.1016/j.pan.2016.05.393 PMID: 27288147 PMCID: PMC5123629

[15] Diana A, Wang LM, D'Costa Z, Azad A, Silva MA, Soonawalla Z, Allen P, Liu S, McKenna WG, Muschel RJ, Fokas E. Prognostic role and correlation of CA9, CD31, CD68 and CD20 with the desmoplastic stroma in pancreatic ductal adenocarcinoma. Oncotarget, 2016, 7(45):72819–72832. https://doi.org/10.18632/oncotarget.12022 PMID: 27637082 PMCID: PMC5341946

[16] Erkan M, Hausmann S, Michalski CW, Fingerle AA, Dobritz M, Kleeff J, Friess H. The role of stroma in pancreatic cancer: diagnostic and therapeutic implications. Nat Rev Gastroenterol Hepatol, 2012, 9(8):454–467. https://doi.org/10.1038/nrgastro.2012.115 PMID: 22710569

[17] Erkan M, Michalski CW, Rieder S, Reiser-Erkan C, Abiatari I, Kolb A, Giese NA, Esposito I, Friess H, Kleeff J. The activated stroma index is a novel and independent prognostic marker in pancreatic ductal adenocarcinoma. Clin Gastroenterol Hepatol, 2008, 6(10):1155–1161. https://doi.org/10.1016/j.cgh.2008.05.006 PMID: 18639493

[18] Erkan M, Reiser-Erkan C, Michalski CW, Deucker S, Sauliunaite D, Streit S, Esposito I, Friess H, Kleeff J. Cancer–stellate cell interactions perpetuate the hypoxia–fibrosis cycle in pancreatic ductal adenocarcinoma. Neoplasia, 2009, 11(5):497–508. https://doi.org/10.1593/neo.81618 PMID: 19412434 PMCID: PMC2671860

[19] Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA. The pancreas cancer microenvironment. Clin Cancer Res, 2012, 18(16):4266–4276. https://doi.org/10.1158/1078-0432.CCR-11-3114 PMID: 22896693 PMCID: PMC3442232

[20] Fujita H, Ohuchida K, Mizumoto K, Nakata K, Yu J, Kayashima T, Cui L, Manabe T, Ohtsuka T, Tanaka M. Alpha-smooth muscle actin expressing stroma promotes an aggressive tumor biology in pancreatic ductal adenocarcinoma. Pancreas, 2010, 39(8):1254–1262. https://doi.org/10.1097/MPA.0b013e3181dbf647 PMID: 20467342

[21] Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov, 2019, 18(3):197–218. https://doi.org/10.1038/s41573-018-0007-y PMID: 30610226

[22] Galon J, Bruni D. Tumor immunology and tumor evolution: intertwined histories. Immunity, 2020, 52(1):55–81. https://doi.org/10.1016/j.immuni.2019.12.018 PMID: 31940273

[23] Genard G, Lucas S, Michiels C. Reprogramming of tumor-associated macrophages with anticancer therapies: radiotherapy *versus* chemo- and immunotherapies. Front Immunol, 2017, 8:828. https://doi.org/10.3389/fimmu.2017.00828 PMID: 28769933 PMCID: PMC5509958

[24] Han H, Hou Y, Chen X, Zhang P, Kang M, Jin Q, Ji J, Gao M. Metformin-induced stromal depletion to enhance the penetration of Gemcitabine-loaded magnetic nanoparticles for pancreatic cancer targeted therapy. J Am Chem Soc, 2020, 142(10):4944–4954. https://doi.org/10.1021/jacs.0c00650 PMID: 32069041

[25] Hartupee JC, Zhang H, Bonaldo MF, Soares MB, Dieckgraefe BK. Isolation and characterization of a cDNA encoding a novel member of the human regenerating protein family: Reg IV. Biochim Biophys Acta, 2001, 1518(3):287–293. https://doi.org/10.1016/s0167-4781(00)00284-0 PMID: 11311942

[26] He XJ, Jiang XT, Ma YY, Xia YJ, Wang HJ, Guan TP, Shao QS, Tao HQ. REG4 contributes to the invasiveness of pancreatic cancer by upregulating MMP-7 and MMP-9. Cancer Sci, 2012, 103(12):2082–2091. https://doi.org/10.1111/cas.12018 PMID: 22957785 PMCID: PMC7659226

[27] Hu H, Hang JJ, Han T, Zhuo M, Jiao F, Wang LW. The M2 phenotype of tumor-associated macrophages in the stroma confers a poor prognosis in pancreatic cancer. Tumour Biol, 2016, 37(7):8657–8664. https://doi.org/10.1007/s13277-015-4741-z PMID: 26738860

[28] Hu H, Tu W, Chen Y, Zhu M, Jin H, Huang T, Zou Z, Xia Q. The combination of PKM2 overexpression and M2 macrophages infiltration confers a poor prognosis for PDAC patients. J Cancer, 2020, 11(8):2022–2031. https://doi.org/10.7150/jca.38981 PMID: 32127930 PMCID: PMC7052945

[29] Infante JR, Matsubayashi H, Sato N, Tonascia J, Klein AP, Riall TA, Yeo C, Iacobuzio-Donahue C, Goggins M. Peritumoral fibroblast SPARC expression and patient outcome with resectable pancreatic adenocarcinoma. J Clin Oncol, 2007, 25(3):319–325. https://doi.org/10.1200/JCO.2006.07.8824 PMID: 17235047

[30] Jones LE, Humphreys MJ, Campbell F, Neoptolemos JP, Boyd MT. Comprehensive analysis of matrix metalloproteinase and tissue inhibitor expression in pancreatic cancer: increased expression of matrix metalloproteinase-7 predicts poor survival. Clin Cancer Res, 2004, 10(8):2832–2845. https://doi.org/10.1158/1078-0432.ccr-1157-03 PMID: 15102692

[31] Karamitopoulou E. Tumour microenvironment of pancreatic cancer: immune landscape is dictated by molecular and histopathological features. Br J Cancer, 2019, 121(1):5–14. https://doi.org/10.1038/s41416-019-0479-5 PMID: 31110329 PMCID: PMC6738327

[32] Katsuta E, Qi Q, Peng X, Hochwald SN, Yan L, Takabe K. Pancreatic adenocarcinomas with mature blood vessels have better overall survival. Sci Rep, 2019, 9(1):1310. https://doi.org/10.1038/s41598-018-37909-5 PMID: 30718678 PMCID: PMC6362082

[33] Kim JH, Shin BC, Park WS, Lee J, Kuh HJ. Antifibrotic effects of Pentoxifylline improve the efficacy of Gemcitabine in human pancreatic tumor xenografts. Cancer Sci, 2017, 108(12):2470–2477. https://doi.org/10.1111/cas.13405 PMID: 28940685 PMCID: PMC5715266

[34] Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM.

Gemcitabine plus Bevacizumab compared with Gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol, 2010, 28(22):3617–3622. https://doi.org/10.1200/JCO.2010.28.1386 PMID: 20606091 PMCID: PMC2917317

[35] Koenig A, Mueller C, Hasel C, Adler G, Menke A. Collagen type I induces disruption of E-cadherin-mediated cell–cell contacts and promotes proliferation of pancreatic carcinoma cells. Cancer Res, 2006, 66(9):4662–4671. https://doi.org/10.1158/0008-5472.CAN-05-2804 PMID: 16651417

[36] Korpanty G, Carbon JG, Grayburn PA, Fleming JB, Brekken RA. Monitoring response to anticancer therapy by targeting microbubbles to tumor vasculature. Clin Cancer Res, 2007, 13(1):323–330. https://doi.org/10.1158/1078-0432.CCR-06-1313 PMID: 17200371

[37] Kuiper P, Hawinkels LJ, de Jonge-Muller ES, Biemond I, Lamers CB, Verspaget HW. Angiogenic markers endoglin and vascular endothelial growth factor in gastroenteropancreatic neuroendocrine tumors. World J Gastroenterol, 2011, 17(2):219–225. https://doi.org/10.3748/wjg.v17.i2.219 PMID: 21245995 PMCID: PMC3020376

[38] Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB. Curcumin potentiates antitumor activity of Gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB-regulated gene products. Cancer Res, 2007, 67(8):3853–3861. https://doi.org/10.1158/0008-5472.CAN-06-4257 PMID: 17440100

[39] Kurahara H, Shinchi H, Mataki Y, Maemura K, Noma H, Kubo F, Sakoda M, Ueno S, Natsugoe S, Takao S. Significance of M2-polarized tumor-associated macrophage in pancreatic cancer. J Surg Res, 2011, 167(2):e211–e219. https://doi.org/10.1016/j.jss.2009.05.026 PMID: 19765725

[40] Lee KY, Cho HD, Hwangbo Y, Yang JK, Han SJ, Choi HJ, Lee YN, Cha SW, Moon JH, Cho YD, Park SH, Lee TH. Efficacy of 3 fine-needle biopsy techniques for suspected pancreatic malignancies in the absence of an on-site cytopathologist. Gastrointest Endosc, 2019, 89(4):825–831.e1. https://doi.org/10.1016/j.gie.2018.10.042 PMID: 30403966

[41] Li N, Li Y, Li Z, Huang C, Yang Y, Lang M, Cao J, Jiang W, Xu Y, Dong J, Ren H. Hypoxia inducible factor 1 (HIF-1) recruits macrophage to activate pancreatic stellate cells in pancreatic ductal adenocarcinoma. Int J Mol Sci, 2016, 17(6):799. https://doi.org/10.3390/ijms17060799 PMID: 27271610 PMCID: PMC4926333

[42] Liu C, Cheng H, Luo G, Lu Y, Jin K, Guo M, Ni Q, Yu X. Circulating regulatory T cell subsets predict overall survival of patients with unresectable pancreatic cancer. Int J Oncol, 2017, 51(2):686–694. https://doi.org/10.3892/ijo.2017.4032 PMID: 28714519

[43] Lum LG, Thakur A, Choi M, Deol A, Kondadasula V, Schalk D, Fields K, Dufrense M, Philip P, Dyson G, Aon HD, Shields AF. Clinical and immune responses to anti-CD3 x anti-EGFR bispecific antibody armed activated T cells (EGFR BATs) in pancreatic cancer patients. Oncoimmunology, 2020, 9(1):1773201. https://doi.org/10.1080/2162402X.2020.1773201 PMID: 32939319 PMCID: PMC7480816

[44] Lunardi S, Muschel RJ, Brunner TB. The stromal compartments in pancreatic cancer: are there any therapeutic targets? Cancer Lett, 2014, 343(2):147–155. https://doi.org/10.1016/j.canlet.2013.09.039 PMID: 24141189

[45] Luo H, England CG, Shi S, Graves SA, Hernandez R, Liu B, Theuer CP, Wong HC, Nickles RJ, Cai W. Dual targeting of tissue factor and CD105 for preclinical PET imaging of pancreatic cancer. Clin Cancer Res, 2016, 22(15):3821–3830. https://doi.org/10.1158/1078-0432.CCR-15-2054 PMID: 27026197 PMCID: PMC4970931

[46] Lutz ER, Wu AA, Bigelow E, Sharma R, Mo G, Soares K, Solt S, Dorman A, Wamwea A, Yager A, Laheru D, Wolfgang CL, Wang J, Hruban RH, Anders RA, Jaffee EM, Zheng L. Immunotherapy converts nonimmunogenic pancreatic tumors into immunogenic foci of immune regulation. Cancer Immunol Res, 2014, 2(7):616–631. https://doi.org/10.1158/2326-6066.CIR-14-0027 PMID: 24942756 PMCID: PMC4082460

[47] Ma X, Wu D, Zhou S, Wan F, Liu H, Xu X, Xu X, Zhao Y, Tang M. The pancreatic cancer secreted REG4 promotes macrophage polarization to M2 through EGFR/AKT/CREB pathway. Oncol Rep, 2016, 35(1):189–196. https://doi.org/10.3892/or.2015.4357 PMID: 26531138

[48] Mace TA, Ameen Z, Collins A, Wojcik S, Mair M, Young GS, Fuchs JR, Eubank TD, Frankel WL, Bekaii-Saab T, Bloomston M, Lesinski GB. Pancreatic cancer-associated stellate cells promote differentiation of myeloid-derived suppressor cells in a STAT3-dependent manner. Cancer Res, 2013, 73(10):3007–3018. https://doi.org/10.1158/0008-5472.CAN-12-4601 PMID: 23514705 PMCID: PMC3785672

[49] Maehira H, Miyake T, Iida H, Tokuda A, Mori H, Yasukawa D, Mukaisho KI, Shimizu T, Tani M. Vimentin expression in tumor microenvironment predicts survival in pancreatic ductal adenocarcinoma: heterogeneity in fibroblast population. Ann Surg Oncol, 2019, 26(13):4791–4804. https://doi.org/10.1245/s10434-019-07891-x PMID: 31583548

[50] Mahajan UM, Langhoff E, Goni E, Costello E, Greenhalf W, Halloran C, Ormanns S, Kruger S, Boeck S, Ribback S, Beyer G, Dombroswki F, Weiss FU, Neoptolemos JP, Werner J, D'Haese JG, Bazhin A, Peterhansl J, Pichlmeier S, Büchler MW, Kleeff J, Ganeh P, Sendler M, Palmer DH, Kohlmann T, Rad R, Regel I, Lerch MM, Mayerle J. Immune cell and stromal signature associated with progression-free survival of patients with resected pancreatic ductal adenocarcinoma. Gastroenterology, 2018, 155(5):1625–1639.e2. https://doi.org/10.1053/j.gastro.2018.08.009 PMID: 30092175

[51] Maimela NR, Liu S, Zhang Y. Fates of CD8+ T cells in tumor microenvironment. Comput Struct Biotechnol J, 2019, 17:1–13. https://doi.org/10.1016/j.csbj.2018.11.004 PMID: 30581539 PMCID: PMC6297055

[52] Miyashita T, Tajima H, Makino I, Okazaki M, Yamaguchi T, Ohbatake Y, Nakanuma S, Hayashi H, Takamura H, Ninomiya I, Fushida S, Kishimoto K, Harmon JW, Ohta T. Neoadjuvant chemotherapy with Gemcitabine plus Nab-Paclitaxel reduces the number of cancer-associated fibroblasts through depletion of pancreatic stroma. Anticancer Res, 2018, 38(1):337–343. https://doi.org/10.21873/anticanres.12227 PMID: 29277792

[53] Nielsen MFB, Mortensen MB, Detlefsen S. Key players in pancreatic cancer–stroma interaction: cancer-associated fibroblasts, endothelial and inflammatory cells. World J Gastroenterol, 2016, 22(9):2678–2700. https://doi.org/10.3748/wjg.v22.i9.2678 PMID: 26973408 PMCID: PMC4777992

[54] Orhan A, Vogelsang RP, Andersen MB, Madsen MT, Hölmich ER, Raskov H, Gögenur I. The prognostic value of tumour-infiltrating lymphocytes in pancreatic cancer: a systematic review and meta-analysis. Eur J Cancer, 2020, 132:71–84. https://doi.org/10.1016/j.ejca.2020.03.013 PMID: 32334338

[55] Özdemir BC, Pentcheva-Hoang T, Carstens JL, Zheng X, Wu CC, Simpson TR, Laklai H, Sugimoto H, Kahlert C, Novitskiy SV, De Jesus-Acosta A, Sharma P, Heidari P, Mahmood U, Chin L, Moses HL, Weaver VM, Maitra A, Allison JP, LeBleu VS, Kalluri R. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell, 2014, 25(6):719–734. https://doi.org/10.1016/j.ccr.2014.04.005 PMID: 24856586 PMCID: PMC4180632

[56] Provenzano PP, Eliceiri KW, Campbell JM, Inman DR, White JG, Keely PJ. Collagen reorganization at the tumor–stromal interface facilitates local invasion. BMC Med, 2006, 4(1):38. https://doi.org/10.1186/1741-7015-4-38 PMID: 17190588 PMCID: PMC1781458

[57] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res, 2014, 74(11):2913–2921. https://doi.org/10.1158/0008-5472.CAN-14-0155 PMID: 24840647

[58] Rataj F, Kraus FBT, Chaloupka M, Grassmann S, Heise C, Cadilha BL, Duewell P, Endres S, Kobold S. PD1–CD28 fusion protein enables CD4+ T cell help for adoptive T cell therapy in models of pancreatic cancer and non-Hodgkin lymphoma. Front Immunol, 2018, 9:1955. https://doi.org/10.3389/fimmu.2018.01955 PMID: 30214445 PMCID: PMC6125378

[59] Sage EH, Bornstein P. Extracellular proteins that modulate cell–matrix interactions. SPARC, tenascin, and thrombospondin. J Biol Chem, 1991, 266(23):14831–14834. PMID: 1714444

[60] Saito K, Matsuo Y, Imafuji H, Okubo T, Maeda Y, Sato T, Shamoto T, Tsuboi K, Morimoto M, Takahashi H, Ishiguro H, Takiguchi S. Xanthohumol inhibits angiogenesis by suppressing nuclear factor-κB activation in pancreatic cancer. Cancer Sci,

2018, 109(1):132–140. https://doi.org/10.1111/cas.13441 PMID: 29121426 PMCID: PMC5765302

[61] Shintani Y, Hollingsworth MA, Wheelock MJ, Johnson KR. Collagen I promotes metastasis in pancreatic cancer by activating c-Jun NH(2)-terminal kinase 1 and up-regulating N-cadherin expression. Cancer Res, 2006, 66(24):11745–11753. https://doi.org/10.1158/0008-5472.CAN-06-2322 PMID: 17178870

[62] Sinn M, Denkert C, Striefler JK, Pelzer U, Stieler JM, Bahra M, Lohneis P, Dörken B, Oettle H, Riess H, Sinn BV. α-Smooth muscle actin expression and desmoplastic stromal reaction in pancreatic cancer: results from the CONKO-001 study. Br J Cancer, 2014, 111(10):1917–1923. https://doi.org/10.1038/bjc.2014.495 PMID: 25314063 PMCID: PMC4229636

[63] Takeuchi Y, Nishikawa H. Roles of regulatory T cells in cancer immunity. Int Immunol, 2016, 28(8):401–409. https://doi.org/10.1093/intimm/dxw025 PMID: 27160722 PMCID: PMC4986235

[64] Tuncyurek P, Mayer JM, Klug F, Dillmann S, Henne-Bruns D, Keller F, Stracke S. Everolimus and Mycophenolate Mofetil sensitize human pancreatic cancer cells to Gemcitabine *in vitro*: a novel adjunct to standard chemotherapy? Eur Surg Res, 2007, 39(6):380–387. https://doi.org/10.1159/000107356 PMID: 17700025

[65] Wang WQ, Liu L, Xu HX, Luo GP, Chen T, Wu CT, Xu YF, Xu J, Liu C, Zhang B, Long J, Tang ZY, Yu XJ. Intratumoral α-SMA enhances the prognostic potency of CD34 associated with maintenance of microvessel integrity in hepatocellular carcinoma and pancreatic cancer. PLoS One, 2013, 8(8):e71189. https://doi.org/10.1371/journal.pone.0071189 PMID: 23940715 PMCID: PMC3734294

[66] Whatcott CJ, Diep CH, Jiang P, Watanabe A, LoBello J, Sima C, Hostetter G, Shepard HM, Von Hoff DD, Han H. Desmoplasia in primary tumors and metastatic lesions of pancreatic cancer. Clin Cancer Res, 2015, 21(15):3561–3568. https://doi.org/10.1158/1078-0432.CCR-14-1051 PMID: 25695692 PMCID: PMC4526394

[67] Xu YF, Lu Y, Cheng H, Shi S, Xu J, Long J, Liu L, Liu C, Yu X. Abnormal distribution of peripheral lymphocyte subsets induced by PDAC modulates overall survival. Pancreatology, 2014, 14(4):295–301. https://doi.org/10.1016/j.pan.2014.05.797 PMID: 25062880

[68] Yoshikawa K, Mitsunaga S, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Aizawa M, Ochiai A. Impact of tumor-associated macrophages on invasive ductal carcinoma of the pancreas head. Cancer Sci, 2012, 103(11):2012–2020. https://doi.org/10.1111/j.1349-7006.2012.02411.x PMID: 22931216 PMCID: PMC7659389

[69] Yoshitomi H, Kobayashi S, Ohtsuka M, Kimura F, Shimizu H, Yoshidome H, Miyazaki M. Specific expression of endoglin (CD105) in endothelial cells of intratumoral blood and lymphatic vessels in pancreatic cancer. Pancreas, 2008, 37(3):275–281. https://doi.org/10.1097/mpa.0b013e3181690b97 PMID: 18815549

[70] Young Bang J, Krall K, Jhala N, Singh C, Tejani M, Arnoletti JP, Navaneethan U, Hawes R, Varadarajulu S. Comparing needles and methods of endoscopic ultrasound-guided fine-needle biopsy to optimize specimen quality and diagnostic accuracy for patients with pancreatic masses in a randomized trial. Clin Gastroenterol Hepatol, 2021, 19(4):825–835.e7. https://doi.org/10.1016/j.cgh.2020.06.042 PMID: 32652307

[71] Yu M, Guan R, Hong W, Zhou Y, Lin Y, Jin H, Hou B, Jian Z. Prognostic value of tumor-associated macrophages in pancreatic cancer: a meta-analysis. Cancer Manag Res, 2019, 11:4041–4058. https://doi.org/10.2147/CMAR.S196951 PMID: 31118813 PMCID: PMC6504556

[72] Zhang A, Qian Y, Ye Z, Chen H, Xie H, Zhou L, Shen Y, Zheng S. Cancer-associated fibroblasts promote M2 polarization of macrophages in pancreatic ductal adenocarcinoma. Cancer Med, 2017, 6(2):463–470. https://doi.org/10.1002/cam4.993 PMID: 28097809 PMCID: PMC5313646

[73] Zhang Y, Choksi S, Chen K, Pobezinskaya Y, Linnoila I, Liu ZG. ROS play a critical role in the differentiation of alternatively activated macrophages and the occurrence of tumor-associated macrophages. Cell Res, 2013, 23(7):898–914. https://doi.org/10.1038/cr.2013.75 PMID: 23752925 PMCID: PMC3698641

[74] Zhou L, Yu L, Ding G, Chen W, Zheng S, Cao L. Over-expressions of DLL4 and CD105 are associated with poor prognosis of patients with pancreatic ductal adenocarcinoma. Pathol Oncol Res, 2015, 21(4):1141–1147. https://doi.org/10.1007/s12253-015-9937-4 PMID: 25986715

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