PANCREATIC STELLATE CELLS: THE TOP MANAGERS OF THE PANCREATIC TUMOR MICROENVIRONMENT

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ABSTRACT. Background Pancreatic stellate cells (PSC), being producers of stromal components, actively interact with cancer cells, determine the formation of a stromal barrier between the latter and thereby provide tumor chemoresistance. Objective The review is devoted to analysis of recent data on the role of stellate pancreatocytes in the formation of the stromal microenvironment of pancreatic tumors, molecular mechanisms through which the regulation and realization of stellate cell functions is carried out. Methods Data processing was carried out by the method of complex material analysis. Results Stellate pancreatocytes (PSC) exhibit phenotypically and functionally two states: inactive and active. PSC activation is carried out by cells of the developing tumor through a variety of molecular mediators. Activation triggers for PSC are Yes-associated protein, TGF-β1, miR-1246, miR-1290, miR-210, CCN2 (connective tissue growth factor), TRPV1, SP and CGRP (Calcitonin gene-related peptide) and many other factors. Conclusion Stellate pancreatic stellate cells, being producers of the interacinar stroma, are activated by various factors (TNF-α, IL-6, MCP-1, ATP, and HMGB1, etc.), including factors produced by tumor cells of the pancreas, and act as regulators of proliferation, migration, and suppression apoptosis of the latter. An increase in the expression of a TGF-β1, a5 integrin receptor ITGA5 (fibronectin receptor), hyaluronic acid, hyaluronan synthase 2 (HAS2), matrix metallopeptidase 2 (MMP2), Nodal protein, miR-1246 and miR-1290, miR-210, CCN2 (connective tissue growth factor), TRPV1, SP and CGRP (Calcitonin gene-related peptide) and many other factors. Key words: stellate pancreatic stellate cells, activation of stellate pancreatic stellate cells, molecular mediators, pancreatic tumor cells, tumor microenvironment.
Introduction

Stellate pancreatic cells (PSC) as cells - promoters of carcinogenesis remained the focus of attention of the scientific community in recent years. PSCs mediate proliferation, migration and suppress apoptosis of pancreatic cancer cells. Also, these cells stimulate the epithelial-mesenchymal transition, the formation of phenotypes of cancer cells similar to stem cells, which increases resistance to the applied therapy, metastasis, and relapses. By acting on endothelial cells, neuroelements, β-cells of the islets PSC induce angiogenesis, neurogenesis, as well as disrupt the functional state and cause apoptosis of β-cells. Stellate pancreatic cells stimulate apoptosis of T cells, suppress the infiltration of tumor tissues by the latter, and can activate histiocytes, thereby modulating the local immune response [1]. Stellate pancreatic cells located between the lobules and covering the pancreatic acini, manifest themselves as pluripotent cells, the activation of which by various factors causes their transformation into myofibroblast-like cells. These cells are the main source of the extracellular matrix proteins synthesis, thereby form fibrotic masses in the tissue of the pancreas. Fibrosis in this case is able to capture the islets, causing the premises for the development of diabetes. As the main producers of the complex microenvironment pancreatic adenocarcinoma stroma, PSCs actively influence the progression of the tumor process and its metastasis [2,3]. By ensuring the deposition of collagen fibers in the interacinar space, PSCs affect the mechanical properties of the pancreatic microenvironment [4]. The stellate cells of the pancreas determine the location of collagen fibers, the adhesion of the latter to other elements of the extracellular matrix, as well as stromal viscosity and elasticity [5]. Similar functions are typical for myofibroblast-like cells [6]. Compaction of the desmoplastic tissue of the pancreas during carcinogenesis can be influenced in order to change its mechanistic properties, which will improve the delivery of chemical agents directly to the tumor [5].

Morphology of PSC and their involvement in carcinogenesis

Morphologically stellate pancreatic cells in cell culture can take the following forms: quiescent flattened cells with lipid inclusions; elongated, angular-looking cells with lipid droplets; cells with dense lipid droplets; activated PSCs with long extensions without lipid droplets [7]. Quiescent desmin-positive PSCs have a polygonal shape, with luminense lipid droplets, and express transcriptional labels, the panel of which changes upon activation and show a lower ability to proliferate and migrate compared to fusiform activated PSC [8]. The further development of events of activated PSC can have two options: the first is the lifelong preservation of the activated status, even in the absence of paracrine activation catalysts, which leads to the formation of pancreatic fibrosis. And the second is to return to the previous quiescent (inactive) state [9]. Indications that the aggregate of PSC cell cultures and pancreatic cancer cells provide an enhancement of the proliferation, migratory and invasive properties, confirm the influence of these cells on the formation and progression of a tumor. Moreover, traces of PSC were found in metastases originating from a pancreatic tumor. These cells should be considered not only as producers of various transmitters-inductors of carcinogenesis but also as regulators of this process. PSC has been shown to induce an increase in resistance to gemcitabine (the drug of choice for chemotherapy) and radiation therapy in cancer cells and demonstrate laminin and fibronectin synthesis, which suppress apoptosis of cancer cells. The synthesis of type I collagen, SPARC, and metalloproteinases 1 and 2 by stellate pancreatic cells, promotes the invasive properties of the tumor by damaging the intercellular substance, which aggravates the prognosis [10]. According to some data, PSC creates about half of the tumor stroma, inducing desmoplasia, remodeling of the extracellular matrix, epithelial-mesenchymal transition, and the spread of the tumor process [11]. Carcinogenesis causes PSC activation, at which cells begin to produce connective tissue components, activation is provided by Yes-associated protein, inhibition of which leads to the deactivation of PSC, while increased expression of Yes-1-associated protein correlates with the expression of SPARC (a protein involved in the interactions of the extracellular matrix connective tissue, cell migration) [12].

Stellate pancreatic cells of the islets of Langerhans

In the endocrine islets of Langerhans, the detected PSCs can rather be considered as a subpopulation [13]. However, PSCs demonstrate the expression of several stem cell markers, which makes it potentially possible for their differentiation, including into islet β-cells, which is confirmed by in vitro experiments [14]. Co-cultivation of PSC and islet cells (Min6 – β-cell culture) reveals increased insulin secretion with a simultaneous decrease in its content in the cells themselves. Also, the combined effect of PSC and Min6 cells on IL6 does not alter either the expression of β-cell specific genes or the expression of miRNA [15]. Lipid loading (lipid intoxication) decreases the expression of ligands associated with lipid metabolism (especially SREBP-1c) in islet stellate pancreatic cells. Stimulation of SREBP-1c expression increases islet viability and ultimately insulin production [16]. In retinol-deficient mice, a change in the shape of the islets is noted, which also demonstrates an increased synthesis of α-actin of smooth muscles, which is characteristic of the increased activity of islet stellate cells. The activation is leveled by the administration of retinol. In a culture of islet stellate cells saturated with retinol, there is an increased expression of CRBP1, a retinol-binding protein, the knockdown of which provides the phenotype of quiescent islet stel-
late cells and thereby reduces their damaging effect on islet function [17].

**Co-cultivation of PSC and adenocarcinoma cells allows to investigate their interactions**

To study the properties, secretome, and involvement of stellate pancreatocytes in signaling pathways, mouse and human panels of immortalized cells are used, which, however, differ in the activity of collagen secretion, response to stimulation of TGF-β, growth rate, and composition of the secretome [18]. Due to the fact that when PSC are isolated from the pancreatic tissue, their activation occurs, the study uses the α-SMA (α-smooth myocyte actin) marker, which is indirect, since it is characteristic not only of activated PSCs but also of myofibroblasts, smooth muscle cells, and pericytes and more characterizes the biotransformation of PSC into myofibroblasts than activation. Another, a more unified indicator of PSC activity is the disappearance of retinoid inclusions, fat-like droplets in the cytoplasm of cells. To assess the purity of a culture, it is advisable to use several markers [19, 20]. Despite some difficulties in isolating pure cultures and discrepancies in growth dynamics, secretory and structural characteristics, primary PSC cell lines isolated from various pathologies, including tumors, can serve as a source of PSC production [21]. It is also possible to obtain a culture of these cells by the growth of stellate pancreatocyte (PSC) and pancreatic tumor cells (PSC) lines from the same tumor sample due to differences in secretions and growth rates. Thus, PSCs exhibit mutations in the KRAS and TP5 proteins, as well as the expression of cytokeratin 19, Ki-67, and p53, while PSCs stably express α-SMA and vimentin. Tumor cells also show a higher growth rate compared to stellate pancreatocytes [22].

**Factors influencing the activation of stellate pancreatocytes**

Damaged acinar cells, immune cells produce cytokines, growth factors that activate stellate pancreatocytes by the paracrine way, which in turn also secrete various modulators by an autocrine way that maintain the activated phenotype of these cells for a long time, which leads to excessive deposition of stromal elements and fibrosis [23]. The PADI 4 enzyme provides the deployment of the extracellular neutrophil trap effect, which leads to the transfer of cytoplasmic proteins and DNA into the extracellular space. The DNA of neutrophils activates the stellate cells of the pancreas, which are involved in fibrosis, promoting the proliferation and metastasis of pancreatic cancer. However, treatment with DNase and removal of the receptor for advanced glycation end products (RAGE) in stellate cells neutralize the stimulating effect of DNA on PSC proliferation and tumor progression [24] (Figure 1).

![Fig.1. Neutrophil extracellular trap PADI 4--enzyme peptidyl arginine deiminase 4, NET–neutrophil extracellular trap.](image)

The effect on PSC activation is claimed by speckle-type POZ protein (SPOP), knockdown of which leads to a progressive increase in the activity of primary PSCs by initiating the nuclear factor-kappa B (NF-κB) / interleukin-6 (IL-6) signaling pathway. Suppression of PSC activation by SPOP may in part depend on the Fas-associated death domain (FADD), which is a substrate for SPOP and activates NF-κB. Activation of the Fas receptor or “death receptor” leads to programmed cell death (apoptosis) [25]. BAG3 secreted by activated PSCs supports the activation of the latter and stimulates the invasion of ductal adenocarcinoma cells through the release of a whole complex of cytokines, as well as through IL-8, MCP1, TGF-β2, and IGFBP2, acting according to a paracrine mechanism in the case of invasion regulation and an autocrine mechanism in the case of PSC activation [26]. PSC activity is also regulated by miRNA let-7d, by inhibiting the activation of these cells through THBS1 (thrombospondin 1) [27]. Determined and other signaling factors causing the activation of stellate pancreatocytes: transforming growth factor β (TGF-β); platelet growth factor; MAPK (mitogen-activated protein kinase); Smads (signaling molecules TGF-β); nuclear factor pathways [28]. Transretinoic acid (ATRA) may trigger the restoration of the dormant state of the PSC by inhibiting the ability of these cells to modify the extracellular matrix [29]. PSCs are also able to respond to mechanical influences that arise as a result of the physical pressure of pancreatic juice, as well as to control mechanostasis both during normal functioning and during the development of fibrosis [30, 31] (Figure 2).
Calcium fluxes as regulators of stellate pancreaticocytes

Stellate pancreaticocytes do not express melatonin receptors. At the same time, thapsigargin, bradykinin, or melatonin are able to change the intracellular concentration of Ca^{2+}, and a change in the melatonin concentration in the presence of indole decreases the ratio of reduced glutathione / oxidized glutathione and increases the formation of reactive oxygen species (ROS) [32]. There is a direct relationship between intracellular Ca^{2+} flow and PSC activation by bradykinin also in the case of acute pancreatitis [33]. The presence of temporary canonical channels of the receptor potential of TRPC1, through which the influx of Ca^{2+} into the PSC is carried out, which causes an increase in physical pressure in the tumor, was determined [34]. PSCs also express KCa3.1 channels, which are also found in tumor cells. KCa3.1 channels are also associated with intracellular Ca^{2+} flow and show interaction with TRPC3 channels. Turning off the activity of the KCa3.1 channel in the PSC suppresses the migration stimulation and chemotaxis by reducing Ca^{2+} and calpain [35]. A decrease in the pH of the intracellular medium suppresses the flow of Ca^{2+} through the Piezo1 channel to the PSC, while the stimulation of this channel by the Yoda1 activator promotes the migration of PSCs in the extracellular space. Piezo1 activation under low pH conditions causes cell death and destruction of PSC spheroids [36]. In the cell culture of stellate pancreaticocytes, exposure to bile acids, sodium cholate, and taurocholate induces a strong influx of Ca^{2+} into the cell, which leads to cell necrosis and death, while the effect on neighboring acinar cells is not too pronounced [37].

Molecular mediators involved in activity of pancreatic stellate cells

In inactive PSCs, albumin is highly expressed and binds to lipid droplets of the retinoid, which also causes the dormancy of these cells and makes them insensitive to the activating effect of TGF-β (β-tumor growth factor). Along with the sedative effect of retinol, artificial promotion of albumin expression leads to a return to the phenotypically quiescent form of PSC and demonstrates the reappearance of lipid inclusions [38]. Stellate pancreaticocytes possess TLRs (TLRs are toll-like receptors that recognize the structures of the bacterial cell wall and trigger the cellular immune response), which makes them one of the players of innate immunity due to their ability to phagocytosis of almost any antigens [39]. Transduced PSCs can secrete CCL22 (chemokine ligand-22 derived from macrophages) and Treg (T cell regulators), inducing T cell apoptosis and creating a unique immune environment around islet cells [40]. The tumor stroma of pancreatic adenocarcinoma exhibits overexpression of the α5 integrin receptor ITGA5 (fibronectin receptor), the overexpression of the latter correlates inversely with the prognosis of survival, since this receptor suppresses PSC differentiation and reduces desmoplasia. This is confirmed by the deactivation of PSC in the case of the use of the peptidomimetic AV3 against ITGA5 [41]. α ITGA11, type 1 collagen receptor, is overexpressed in the stroma of adenocarcinoma of the pancreas, is absent in a healthy gland, and is reduced in adjacent healthy areas of the gland. Activated PSCs increase the regulatory properties of α ITGA11, while knockdown inhibits TGF-β- and PANC-1 CM-mediated activation of stellate pancreaticocytes both at the gene level and at the level of extracellular matrix protein, cytokines, and adhesion molecules, which indicates the key role of α ITGA11 in PSC differentiation and paracrine effects [42]. Hyaluronan (hyaluronic acid) is excessively expressed by activated PSCs, but much less in quiescent PSCs and pancreatic tumor cells. Moreover, activated PSCs produce hyaluronan synthase 2 (HAS2) as well as hyaluronidase 1 (HYAL1) [43]. Increased expression of matrix metallopeptidase 2 (MMP2) in adenocarcinoma tissues may be due to PSC activation, which also promotes invasion and metastasis [44]. Inactive PSCs also produce metalloproteinases (MMPs), including MMP-2, MMP-9, and MMP-13, and, as evidence of autoregulation, inhibitors of these proteinases, which indicates their main function of maintaining the balance of extracellular matrix elements [45]. Stellate pancreaticocytes express Nodal protein, thereby creating paracrine conditions for the vital activity of pancreatic stem cells, as the
main source of tumor development. Nodal protein acts through a paracrine mechanism on Activin at the tumor-stroma interface [46]. Cancer pancreatocytes progressively increase the expression of miR-1246 and miR-1290 in stellate pancreatocytes, which leads to a subsequent increase in the expression of α-smooth muscle actin [47]. In activated PSCs, increased regulatory activity of miR-210 is noted, which is associated with hypoxia. The activity of miR-210 is suppressed by inhibitors of the ERK and PI3K / Akt pathways, which in turn decreases the migration ability, the expression of vimentin, snai-1, and increases the plasmalemma-associated expression of β-catenin in cancer cells that were co-cultured with PSC [48].

With the development of pancreatic fibrosis in activated stellate pancreatocytes, the expression of CCN2 (CCN2 or CTGF – connective tissue growth factor), which is involved in the excessive production of extracellular matrix components, is increased. The expression of CCN2 is carried out through microRNA-21 (miR-21), which is also detected in high amounts in PSC, and the mutual influences of CCN2 and miR-21 are carried out according to the principle of positive feedback, the so-called positive feedback loop; and the substrates themselves are packed into exosomes that can be absorbed by other PSCs [49].

When PSC is stimulated by the transforming growth factor TGF-β1, MIAT is activated in combination with increased levels of α-SMA, collagen I, and COX2; at the same time, miR-216a-3p is suppressed [50]. An increase in miR-21 / miR-221 expression was revealed during two-way communication between PSC cells and cancer-associated fibroblasts, cancer cells, which may be responsible for the progression of the tumor process [51].

In general, the entire process of response, the interaction of stromal cells and tumor cells is reflected in the unfolded protein response (UPR), a complex signaling interaction in which the cellular response to molecular imbalance occurs [52]. A genome study of BXPC-3 cell culture, a human pancreatic cancer cell line often used to study adenocarcinoma, revealed 10 actively expressed genes: TP53, SRC, IL6, JUN, ISG15, CAD, STAT1, OAS3, OAS1, VIM when co-cultured with PSC, which can be used to study the interaction between adenocarcinoma cells and PSC in the neoplastic process [53]. The identification of signaling pathways and molecules that mediate these pathways is extremely important for the development of anti-fibrotic therapy. The Yes-associated protein, the major molecular transmitter of the Hippo pathway, is overexpressed in activated PSCs in the event of an inflammatory or neoplastic process in murine and human cell cultures and is a forward in maintaining an activated PSC profile. Several factors of the MAPK pathway, such as p38, reduce YAP levels in the PSC. YAP knockdown inhibits the activation of Akt and ERK and also suppresses the expression of fibrous and inflammatory proteins both with and without stimulation of TGFβ1 stellate pancreatocytes [54]. Quiescent PSCs have receptors for cholecystokinin, and upon binding, they react with the release of acetylcholine, which in turn acts on cells of the pancreatic acinus [55]. PSC produces the essential acid alanine, which is used to fuel the tricarboxylic acid cycle, reducing the latter’s dependence on glucose and glutamine. Tumor cells, gradually fenced off from the vessels by the forming stroma, also switch to this type of fuel due to the accessiblity of glucose and other nutrients. Thus, alanine secreted by PSC plays a key role in maintaining the vital activity of cancer cells, which in turn stimulate the process of autophagy in stellate pancreatocytes, without which alanine synthesis would be impossible [56].

**Conclusion**

Stellate pancreatocytes, being the leading producers of the tumor microenvironment stroma, are preliminarily subjected to activation by the cancer cells themselves through several mediators and certain signaling pathways, creating favorable conditions for maintaining vital activity, proliferation, invasion, and migration of neoplastic process cells. So, in particular, by counteracting immunocompetent cells, by secretion of CCL2 (chemokine ligand-22) inducing T cell apoptosis, stellate pancreatocytes provide tumor immunoresistance. The PSC ability to produce alanine, which replaces glucose in the Krebs cycle, ensures tumor cells’ functioning and prosperity in conditions of increasing trophic deficiency due to the forming stromal barrier. While remaining “interested” in the activity of stellate pancreatocytes, tumor cells interact with the latter in every possible way, ensuring active proliferation and other “problems” associated with the neoplastic process. Tumor stroma demonstrates high expressions of α ITGA 11 ( type I collagen receptor), α5 integrin receptor ITGA5 (fibronectin receptor), which maintain PSC activated status. Overexpression of metallopeptidases (MMP-2, MMP-9 and MMP-13) in tumor tissue may be caused by PSC activation too. Also in the case of neoplasia, PSC show increase expression of Nodal protein, miR-1246, miR-1290, and miR-210 that indicates active stroma formation. The forming stroma restricts the access of chemotherapy drugs to the tumor, thereby creating chemoresistance. However, the search for ways to influence stellate pancreatocytes through the control of mediators of their activation, or participants in signaling pathways involved in activation processes, creates an opportunity to resist one of the most aggressive tumors of the human body, as a maximum, and reduce its chemoresistance as a minimum. The review is the first part of a series of articles devoted to the modern understanding of the role of stellate pancreatocytes in the neoplastic process of the pancreas and provides, in the future, further study of the mechanisms of interaction of these cells with pan-
cretic tumor cells.

**Information about conflicts of interest**
Potential or explicit conflicts of interest related to this manuscript do not exist and are not foreseen at the time of publication.

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останніх. У пухлиної тканини спостерігається збільшення експресії α ITGA 11 (рецептор коллагену 1 типу), рецептора інтегріна α5 ITGA5 (рецептор фібронектину), металлопептидаз, білка Nodal, miR-1246, miR-1290 та miR-210, що вказує на активацію цих клітин. Підтримка активного стану PSC забезпечується пухлинними клітинами, для яких зірчасті панкреацити є партнерами в прогресуванні неопластичного процесу. Подальше вивчення механізмів взаємодії в системі PSC-пухлинні клітини створює перспективу виявлення важливих впливів на патогенез пухлин підшлункової залози.

**Ключові слова:** зірчасті панкреацити, активізація зірчастих панкреацитів, молекулярні медіатори, пухлинні клітини підшлункової, мікроокруження пухлин.

Станіщенська Н.В. Зв'язують панкреацити: ведуче менеджери микроокруження опухолі підшлункової желези.

**РЕФЕРАТ. Актуальність.** Зв'язують панкреацити, являються клетками - продуцентами компонентів строми активно взаємодіють з раковими клетками, детермінують формування стромального бар'єра між послідовними і тем самим забезпечують химорезистентність опухолі. Це дозволяє посягнення аналізу послідовних даних о ролі зв'язуючих панкреацитів в формуванні стромального мікроокруження опухолей підшлункової желези, молекулярними механізмами, посередником з яким здійснюється регуляція і реалізація функції зв'язуючих клеток. Методи Обработка даних, що здійснювалася методом комплексного аналізу матеріалу. **Результати.** Зв'язують панкреацити з PSC (PSC) доказують фенотипичною та функціональною дво серед значущих: неактивне і активне. Активізація PSC існує клетками формуючимся опухолі посередником целого ряду молекулярних медіаторів. Триттерами активізації для PSC виступають Yes-асоційований білок, TGF-β1, miRNA let-7d, IL-8, MCP1, TGF-β2 і IGFBP2 і інші. В зв'язуючих панкреацитах виявлено 10 активно експресовані генов: TP53, SRC, IL-6, JUN, ISG15, CAD, STAT1, OAS2, OAS3, VIM при використанні культуриїння линії ракових клеток (PCC) з PSC. Декомпозиція PSC закріплена за медіаторами POZ спек-типа (SPOP) активним через енергетичний фактор-KarppaB, за трансертиневою кислотою (ATRA). Появляюча свою активності PSC, експресують значну кількість стовлових клейків, α-SMA (α-актин гладких міоцитов), вімінтен, α ITGA 11 (рецептор коллагена 1 типу), α5 рецептор інтегріна ITGA5 (рецептор фіброберета), гіалуронову кислоту, гіалуронанінтензазу 2 (HAS2), гіалуроніндазу 1 (HYAL1), BAG3, матриксну металлопептидазу 2 (MMP2), Nodal протеїн, miR-1246 та miR-1290, miR-210, CCN2 (connective tissue growth factor, фактор роста соединительной ткани), TRPV1, SP та CGRP (Calcitonin gene-related peptide, пептид відповідний геном кальцитоніна) і багатьох інших субстанцій. **Висновки.** Зв'язують панкреацити, являючись продуктами межакріимальної строми, активирують різними факторами (TNF-α, IL-6, MCP-1, ATP і HMGB1 і ін.); включаючи факторами, секретируемими опухолью клетками підшлункової желези, та відбиваючи як регулятори пролиферації, міграції і подавлення апоптози послідовних. В опухольовій тканині набувається діагностика експресії α ITGA 11 (рецептор коллагена 1 типу), рецептора інтегріна α5 ITGA5 (рецептор фіброберета), металлопептидаз, білка Nodal, miR-1246, miR-1290 та miR-210, що вказує на активну роль цих клейків. Підтримка активного стану PSC забезпечується опухольами клейків, для яких зв'язують панкреацити явища партнерами в прогресуванні неопластичного процесу. Дальнішее изучение механизма взаємодействия в системе PSC-опухоль клеток создает перспективу выявления цирукаг влияния на патогенез опухолей підшлункової желези.

**Ключове слово:** зв'язують панкреацити, активация зв'язующих панкреацитов, молекулярные медиаторы, опухоль клетки підшлункової, микроокружения опухоли.