N.V. Stanishevska

Dnipro State Medical University, Dnipro, Ukraine

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SIGNALING PATHWAYS INVOLVED IN PANCREATIC STELLATE CELLS ACTIVITY AND INTERACTION WITH PANCREATIC CANCER CELLS

Stanishevska N.V. ✉ Signaling pathways involved in pancreatic stellate cells activity and interaction with pancreatic cancer cells.
Dnipro State Medical University, Dnipro, Ukraine.
ABSTRACT. Background. The activation, proliferation and migration capabilities of stellate pancreatocytes are guaranteed by a number of signaling molecular mechanisms that support the interaction of tumor cells with the PSC and determine the neoplastic process. **Objective** The review is a continuation of ат articles series devoted to the modern understanding of the role and functions of stellate pancreatocytes, namely, their involvement in interaction with cancer cells and signaling molecular pathways that provide synergism of the stellate pancreatocyte-cancer cell system. **Methods.** Data processing was carried out by the method of complex material analysis. **Results.** The Hedgehog signaling pathway provides interaction between PSC and tumor cells, which involves the leading mediator of this pathway - sHH (sonic hedgehog), the overexpression of which is recorded in the tumor tissue of the pancreas and ensures the formation of the tumor stroma. Stellate pancreatocytes also trigger the HGF / c-Met / survivin signaling pathway for invasion and metastasis. The activation of the PSCs themselves may be mediated by serotonin via the RhoA / ROCK signaling pathway. While the proliferation and migration of these cells, activated by alcohol, HNE (human neutrophil elastase), PDGF, IL-33 PSC are regulated by the MAP kinase and PI3K pathways. The Wnt signaling pathway promotes collagen accumulation. Through the AMPK / mTOR pathway, factor FTY720 induces apoptosis and inhibits the autophagy of stellate pancreatocytes. The interaction of PSC and tumor cells is also mediated through Notch and TGF-β, and through the Hippo signaling pathway with the participation of YAP / TAZ factors, it is possible to suppress the fibrotic activity of PSC. The interaction of stellate pancreatocytes and tumor cells is reflected in a direct correlation between a decrease in autophagy and apoptosis of stellate pancreatocytes and suppression of invasion and migration of tumor cells. This interaction can be mediated by ERK1 / 2 kinase. Among the factors secreted by tumor cells and causing PSC activation are: growth factor β1 (TGF-β1), PAI-1 protein, translation initiation factor 4E (eIF4E), sHH (involving PSC in pain deployment), Exo-Pan and Exo-Mia exosomes (engaging PSCs in carcinogenesis). Deactivation is mediated by colony stimulating factor 1 (CSF1R, cytokine). In turn, stellate pancreatocytes secrete the chemokine CXCL1, which stimulates the migration and invasion of tumor cells, exosomes with multiple miRNAs, which stimulate the proliferation and migration of cancer cells. **Conclusion**. The activation of stellate pancreatocytes, which is necessary for the implementation of their fibrotic functions, is mediated through the RhoA / ROCK signaling pathway via serotonin. The Hippo pathway (activation) and AMPK / mTOR (suppression of autophagy and activation of apoptosis) are also involved in the regulation of the activity of stellate pancreatocytes. The interaction between the tumor cell and stellate pancreatocyte occurs through the Hedgehog, Notch, and TGF-β signaling pathways; regulation of invasion and metastasis of cancer cells provides the HGF / c-Met / survivin signaling pathway.
Key words: stellate pancreatocytes, pancreatic tumor cells, tumor microenvironment, signaling pathways, chemoresistance.

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Stanishevska N.V. 0000-0002-3029-050X
✉ natstanishevska3536@gmail.com

Introduction

The role of stellate pancreatocytes in tumor formation is manifested in their effect on the proliferation, migration and suppression of apoptosis of

pancreatic cancer cells. The epithelial-mesenchymal transition, the formation of the stem-type fenotype of cancer cells are also mediated by the effects of PSC, which, in turn, increases tumor malignancy and resistance to chemotherapy. Among other influences of these cells, one can also highlights the effect on endothelial cells, neuroelements, β-cells of the islets, which, accordingly, determines their participation in angiogenesis, neurogenesis, dysfunction, and subsequent apoptosis of β-cells. Simultaneously, PSC induce apoptosis of T-lymphocytes and reduce their infiltration of tumor tissue [1]. Stellate pancreatocytes play the role of pluripotential cells, which are characterized by transformation into myofibroblast-like cells. Acting as the main producers of PSC extracellular components, they determine the fibrosis of the pancreatic tissue, which can also involve islets, which creates conditions for the development of diabetes mellitus. By creating a stromal microenvironment of an emerging tumor, PSCs actively influence the development of the tumor process and metastasis [2, 3]. The synthesis of collagen fibers by stellate pancreatocytes determines the density of the tumor tissue, and the spatial arrangement, adhesion of these fibers to other components of the stroma determines its viscosity and elasticity [4, 5]. Point effects on the PSC can control the process of compaction of the desmoplastic tissue of the pancreas, which will lead to changes in its mechanistic properties and will improve the delivery of chemical agents directly to the tumor [5]. In this regard, the identification of signaling pathways and molecules that mediate these pathways is extremely important for the development of anti-fibrotic therapy [6].

Signaling pathways supporting by pancreatic stellate cells

The sHH (sonic hedgehog) signaling pathway initiates the formation of pain in stellate pancreatocytes, with an increase in the expression of TRPV1 (non-selective cation channel, capsaicin receptor). In PSC, the expression and production of TRPV1, SP and CGRP (Calcitonin gene-related peptide) are increased due to the induction of NGF (nerve growth factor) and BDNF (brain-derived neurotrophic factor). Inhibition of the sHH or NGF pathway decreases the production of TRPV1, SP, and CGRP, while disabling NGF and TRPV1 significantly reduces the pain response to mechanical stimulation [6]. Sonic hedgehog (SNH), being the leading factor in the signaling pathway of Hedgehog, is overexpressed by tumor cells of pancreatic adenocarcinoma and performs an executive function in the formation of the stroma of the tumor microenvironment. Switching off the SHH gene led to a decrease in stromal deposits, however, at the same time, the tumors showed increased aggressive properties, proliferation and vascularization. At the same time, the administration of a VEGFR (vascular endothelial growth factor receptor) blocker partially increases the survival rate of an SNH-deficient tumor, which indicates that the tumor stroma inhibits the progression of the neoplastic process [7]. Signaling pathways in PSC and in neighboring acinar cells differ significantly, and stellate pancreatocytes have the ability to generate nitric oxide (NO) in response to stimulating Ca^{2+} signals. In comparison with acinar cells, stellate pancreatocytes show more pronounced Ca^{2+} - mediated NOS-dependent NO signals; in parallel, suppression of NO production protects PSC and acinar cells from necrosis [8]. HGF (hepatocyte growth factor) secreted by PSC increases invasion and metastasis through the HGF / c-Met / survivin pathway, which is negatively regulated by P53 / P21 [9]. PSC activation can be mediated by serotonin, which triggers the RhoA / ROCK signaling pathway. In this case, nuclear translocation of NF-κB and expression of α-SMA (α-actin of smooth myocytes) automatically occur, which aggravates the inflammatory process and fibrosis in the pancreas [10] (Figure 1).

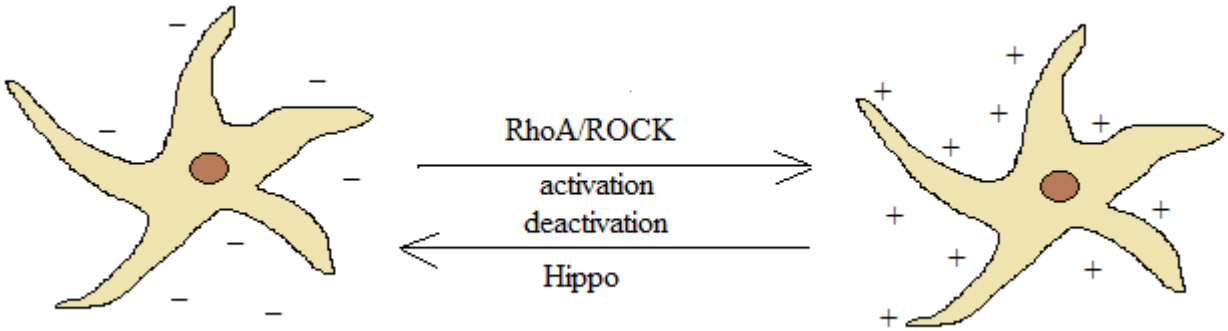

Fig. 1. Signaling pathways involved in pancreatic stellate cells activation and deactivation.

The Rho / myocardin-related transcription factor (MRTF) signaling pathway involved in PSC activation is inhibited by the CCG-222740 molecule, which also inhibits stellate pancreatocytes in vitro and in vivo by decreasing the expression levels of α-SMA (α-smooth muscle cell actin) [11]. PSC proliferation and migration processes stimulated by alcohol, HNE (human neutrophil elastase), PDGF, IL-33

and other cytokines are regulated by the MAP kinase and PI3K pathways. Also, activation of the Indian Hedgehog (IHH) signaling pathway provides migration, proliferation of these cells and collagen deposition. The Sonic Hedgehog (SHH) signaling pathway determines the invasion and migration of tumor cells during their interaction with stellate pancreatocytes. Transmission via the Wnt signaling pathway promotes collagen deposition and cancer progression [12]. Overexpression of SHH in tumor cells is involved in perineural invasion and may serve as an important marker of the progression of neoplastic formation and induces Hedgehog in the PSC, which is necessary for perineural migration of tumor cells [13]. Inhibition of the Hedgehog and CXCR4 pathways prevents the chemoresistance that occurs when PSC and tumor cells are co-cultured, while simultaneously returning to normal cancer cell gene expression altered during co-culture. It seems possible to use a CXCR4 antagonist (AMD3100) or a Hedgehog inhibitor (GDC-0449) in combination with gemcitabine, which reliably demonstrates a slowdown in tumor growth [14]. PSC deactivation can be performed by FTY720, which is also credited with the ability to induce apoptosis and inhibit PSC autophagy through the AMPK / mTOR pathway and thereby suppress the viability, proliferation, and migration of these cells [15] (Figure 2).

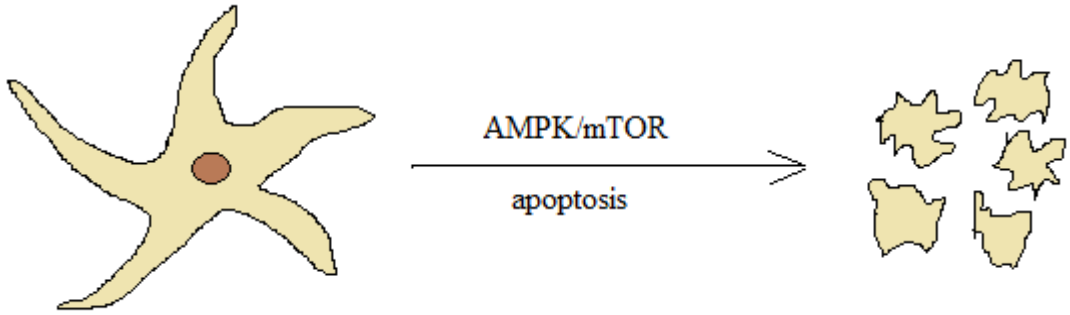

Fig.2. Signaling pathways involved in pancreatic stellate cells apoptosis.

Desmoplasia in pancreatic cancer is the result of activation of stellate cells in response to paracrine stimulation of the tumor epithelium. In turn, PSCs produce a significant number of triggers that provide bidirectional interaction between the tumor and stellate cells. This interaction is mediated by a number of pathways, including Hedgehog, Notch, and TGF-β [16]. One of the options for anti-fibrotic and mechanomodulating effects is the possibility of influencing YAP / TAZ transmitters through the Hippo signaling pathway. YAP / TAZ exhibit the ability to affect the cytoskeleton, initiate stem-like behavior in cells, and modify the stroma and regenerative qualities of cells [17] (Figure 3).

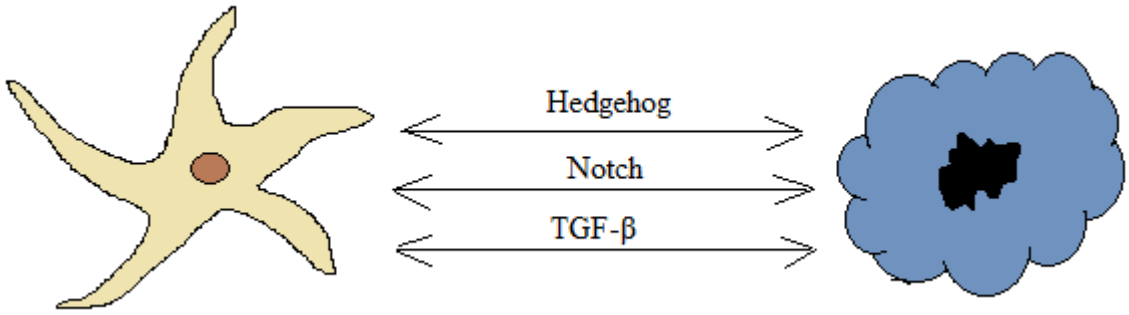

Fig.3. Signaling pathways involved in tumor cell and stellate pancreatocyte interaction.

Interactions between stellate pancreatic cells and tumor cells

The interaction of stellate cells of the pancreas with cancer cells, stromal cells such as immune, endothelial and neuronal forms a special microenvironment for a developing tumor [18]. When the cell culture of pancreatic cancer cells is treated with glutaminase inhibitors, a decrease in autophagy and apoptosis in stellate pancreatocytes is observed, while the proliferation and invasion of cancer cells are suppressed, which is confirmed by increased secretion of Atg5, Bax and Bid proteins in a culture not treated with glutaminase inhibitors, and Bid family proteins in a cell culture incubated by them [19]. In addition to stimulating the proliferation and metastasis of adenocarcinoma cells, stellate cells also decrease the number of immune cells CD8 T, CD4 T cells, NK cells, and M1 macrophages in tumor tis-

sue, while increasing suppressive T cells and M2 macrophages [20]. Tumor tissue stellate pancreatocytes show high expression of fibroblast activation protein α (FAPα), which is associated with lymph node metastases and low survival. PSCs activated by cancer cells, together with FAPα, release the chemokine CXCL1, which leads to phosphorylation of tyrosine kinase receptors EphB1 and EphB3 in tumor cells, ensuring their invasion and migration [21] (Figure 4).

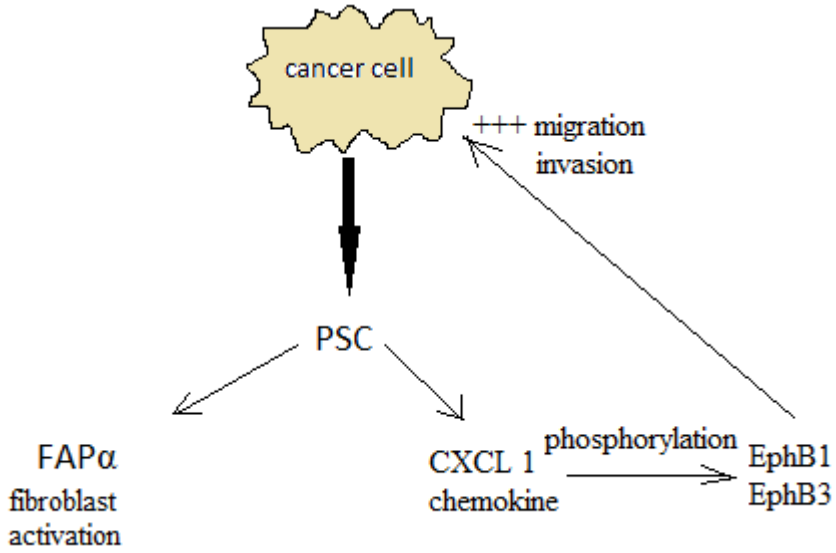

Fig.4. Interaction between pancreatic cancer cell and pancreatic stellate cell FAPα–fibroblast activation protein, CXCL1–chemokine of CXC family, EphB1, EphB3– tyrosine kinase receptors of pancreatic cancer cell.

Tumor tissue shows a strong correlation between the expression of α-SMA and the PAI-1 protein, which is likely to activate PSC. Activation of PAI-1 itself is possible through the action of KRAS (protooncogene) through the ERK, while inhibition of LRP-1, ERK, and c-JUN negates the effect of PAI-1 [22]. The Hic-5 gene is actively expressed by PSC in pancreatic cancer and can be inhibited by siRNA transfection, which significantly reduces the proliferation, invasive and migratory abilities of cancer cells, while increasing their apoptosis. In addition, suppression of Hic-5 in parallel reduces the expression of matrix metalloproteinase-9 (MMP-9). [23] There is a decrease in the viability of PSC and cancer cells after application of plasma phosphate buffered saline (pPBS), which induces immunogenic death of these cells. Also, cancer cells exposed to pPBS were actively phagocytosed by dendritic cells [24]. Intercellular interactions in the cancer cell – stellate cell system determine the epithelial-mesenchymal transition, which ensures the progression of the disease. Spheroids of heterotypic cells, which include ductal carcinoma cells, primary sarcomatoid cells, and PSCs, can be used to study the intercellular interactions of PSCs and tumor cells. The localization of PSCs in the mass of the spheroid depended on the cell line and was either centrally located or evenly distributed. The difference in the expression levels of E-cadherin and vimentin determined different stimulation of the extracellular matrix in different spheroids. Thus, the stromal effect during co-cultivation depends on the composition of the cell line [25]. A study of the effect of ERK1 / 2 kinase on the interaction of tumor cells with stromal cells revealed the expression of p-ERK1 / 2 in both populations, which was more pronounced in PSC-associated cancer cells than in normal PSC and cancer cells. This also explained the high sensitivity of PSC-associated cells to the p-ERK1 / 2 inhibitor, which was associated with the activation of senescence promoters, PSC autophagy associated with cancer cells [26]. Growth factor β1 (TGF-β1) secreted by pancreatic cancer cells and activating PSC is regulated by CCAAT / enhancer binding protein δ (CEBPD) by regulation of the reciprocal loop. The released HDGF (hepatoma growth factor gene) under hypoxic conditions under the influence of factor-1α (HIF-1α) promotes antiapoptosis of PSC and thereby promotes the production and deposition of proteins that stabilize tumor foci. This forms the determination of a novel CEBPD / HIF-1α / HDGF pathway that regulates PSC activity [27]. The study of the PSC secretome revealed that a large number of cellular proteins are controlled by the eukaryotic translation initiation factor 4E (eIF4E), the synthesis of which is triggered in tumor cells grown in the secretion of activated PSCs. Moreover, inhibition of siRNA eIF4E inhibited the proliferation of tumor cells in vitro [28].

The interaction of pancreatic cancer cells with stellate cells is also mediated by exosomes such as Exo-Pan and Exo-Mia, which are produced by cancer cells and involve PSCs in carcinogenesis. This process is mediated by the transfer of the protein from exosomes Lin28B into recipient cells in order to activate the Lin28B / let-7 / HMGA2 / PDGFB

pathway, which may contribute to the formation of distant tumor metastases [29]. Exosomes produced by PSC can also contain many different miRNAs, including miR-21-5p (known as a promoter of metastases), and are able to stimulate the proliferation, migration, and expression of mRNA ligands 1 and 2 chemokines in pancreatic cancer cells [30]. Exosomes produced by pancreatic cancer cells stimulate proliferation, migration, and activate the ERK and Akt signaling pathways, the expression of α-smooth muscle actin (ACTA2) mRNA and genes associated with fibrosis, as well as the production of type I procollagen C-peptide [31].

A more malignant neoplastic process is characterized by less deposition of collagen elements. Ductal adenocarcinoma cells inhibit the expression of ACTA2 (α-actin of smooth myocytes) and COL1A1 (collagen type 1) in stellate pancreatocytes and thereby reduce proliferation. Tumor cells also inactivate PSC via the mediator colony-stimulating factor 1 (CSF1R, cytokine), and suppression of its CSF1R receptor in stellate pancreatocytes blocks this effect. Targeting this receptor makes it possible to maintain the tumor microenvironment and inhibit its development [32].

When PSC and pancreatic adenocarcinoma tumor cells are co-cultured with PSME3 off (a proteasome subunit expressed in various forms of cancer), tumor cells suppress TGF β 1, thereby inhibiting PSC proliferation. Regulation of TGF β 1 PSME3 production is carried out by suppressing activation protein-1 (AP-1) [33]. Sequestosome-1 (sqstm1) or ubiquitin-binding protein p62, which binds proteins for subsequent autophagy, is expressed in reduced amounts by activated PSCs in pancreatic adenocarcinoma. In the experiment, when sqstm1 is suppressed by shRNA in PSC, these cells are transformed into senescent and inflammatory types with increased expression of IL8, CXCL1 and CXCL2 (ligands of chemokines that attract neutrophils). PSC with inhibited sqstm1 stimulates tumor growth, promotes invasion and transformation of macrophages [34].

The interaction between PSCs and adenocarcinoma cells can be blocked by the recently identified factor SB525334, which is a potential and selective inhibitor of TGF-β and affects the transmission of signaling stimuli from PSCs to pancreatic adenocarcinoma cancer cells [35].

Therapeutic targets and chemoresistance

Stellate cells play a key role in the formation of the stroma of a pancreatic tumor, and make up half of all cells of the connective tissue component of the tumor. PSCs actively interact with cancer cells and other cellular structures of the stroma, which together leads to tumor progression [36, 37]. In this regard, the search for therapeutic agents targeting PSCs as the main regulators of fibrosis continues [38]. Signaling molecules such as PPAR-gamma, Rho / Rho-kinase, nuclear factor-kappaB (NF-kappaB), mitogen-activated protein (MAP) kinase, phosphatidylinositol-3-kinase (PI3K), Sma - and Mad-related proteins, as well as reactive oxygen species (ROS) can serve as targets in anti-fibrotic therapy [39].

The elucidation of the mechanisms of interaction between PSC and pancreatic cancer cells, as well as the mechanisms of fibrosis, arouses interest in the search for modulators of these processes with a further prospect of application in therapy. Saicosaponin d (SSd) is able to suppress PSC activation and autophagy by activating the PI3K / Akt / mTOR pathway while suppressing the TGF-β1 / Smads pathway, thereby reducing collagen secretion, causing degradation of the extracellular matrix, and as a consequence, preventing pancreatic tissue fibrosis [40]. Tamoxifen, being an estrogen receptor agonist, is able to rebuild the tumor microenvironment using the mechanism mediated by GPER (G-protein associated with the estrogen receptor) and suppress PSC differentiation into myofibroblasts, active collagen producers [41]. Pantoprazole is able to reduce the secretion of collagen by stellate cells. [42] Penicillin G is able to activate stellate pancreatocytes, which is manifested by an increase in the secretion of fibrosis factors such as TGF-β1 and metalloproteinase-2. The preliminary suppression of the TGF-β1 receptor counteracted the effect after administration of penicillin G, which indicates the involvement of the TGF-β1 signaling pathway in this fibrotic process [43]. The problem of delivery of chemotherapy drugs, as well as an insertion peptide (pHLIP - a peptide with a low pH, allows targeting tissue cells with a low pH of the extracellular matrix) delivering magnetic nanoparticles can be solved by preliminary administration of metformin, which suppresses the expression of TGF-β, the leading ligand of fibrosis after 5 ' - adenosine monophosphate-activated protein kinase pathway (PANC-1) [44]. Inhibitors of the renin-angiotensin system also directly affect islet fibrosis, in which stellate pancreatocytes are actively involved in type 2 diabetes, namely, activation of the renin-angiotensin system in the islets disinhibits (activates) PSCs, stimulates their proliferation, and promotes the formation of fibrous tissue [45]. On co-cultured cancer cells and PSCs, liragludid (an anticancer drug) demonstrates a significant reduction in tumor migration and invasion [46]. In co-cultivation with tumor cells, the effect of gemcitabine demonstrated different degrees of cell resistance, which manifested itself in varying degrees of increased phosphorylation of ERK1 / 2, while 796 proteins were detected in the PSC secretome, including extracellular matrix proteins, fibronectin and collagens. However, these proteins had no effect on the ability of tumor cells to adhere to gemcitabine. However, a fibronectin inhibitor suppresses PSC-mediated chemoresistance to gemcitabine through inhibition of ERK1 / 2 phosphorylation [47]. The stromal microenvironment of pancreatic adenocarcinoma, consisting of PSC, fibroblasts, pro-

tects tumor cells from the effects of gemcitabine (a chemotherapeutic anticancer agent) by producing deoxycytidine and other deoxynucleosides that inhibit the metabolism of gemcitabine, resulting in a decrease in the effect of this drug [48].

Conclusion

Stellate pancreatocytes, being the leading producers of components of the extracellular matrix, and, accordingly, regulators of the fibrosis intensity, mediate their functions, interactions with tumor cells through a number of signaling pathways, the determination of which opens up prospects for their control. Interaction cancer cell-stellate pancreatocyte is provided by signaling pathways Hedgehog, Notch, and TGF-β; the HGF / c-Met / survivin signaling pathway demonstrates regulation of invasion and metastasis of cancer cells. The fibrosing functions of stellate pancreatocytes are realized after their activation, which is provided by the RhoA / ROCK signaling pathway by serotonin. Suppression of the activity of stellate pancreatocytes using YAP / TAZ mediators occurs via the Hippo signaling pathway, while the induction of apoptosis and suppression of autophagy of stellate cells is realized through the AMPK / mTOR pathway using the FTY720 factor, which directly correlates with the suppression of invasion and migration of tumor cells.

Conflicts of interest

All authors declare no conflicts of interest in this paper.

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Станішевська Н.В. Сигнальні шляхи, що залучені в діяльність зірчастих панкреатоцитів та взаємодію з раковими клітинами підшлункової залози.

РЕФЕРАТ. **Актуальність.** Активація, проліферація і міграційні можливості зірчастих панкреатоцитів (PSC) забезпечуються сигнальними молекулярними механізмами, що підтримують взаємодію пухлинних клітин із PSC і детермінують неопластичний процес. **Мета.** Огляд є продовженням серії статей, присвячених сучасному уявленню про роль та функції зірчастих панкреатоцитів, а саме їх залученню у взаємодію із раковими клітинами та сигнальним молекулярним шляхам, що забезпечують синергізм системи зірчастий панкреатоцит-ракова клітина. **Методи**. Обробка даних здійснювалася методом комплексного аналізу матеріалу. **Результати**. Сигнальний шлях Hedgehog забезпечує взаємодію PSC і пухлинних клітин, в якому задіяний провідний медіатор цього шляху - sHH (sonic hedgehog), надекспресія якого реєструється в пухлинній тканині підшлункової залози і забезпечує формування строми пухлини. Зірчасті панкреатоцити запускають також сигнальний шлях HGF / c-Met / сурвівін, що забезпечує інвазію і метастазування. Активація самих PSC може бути опосередкована серотоніном через сигнальний шлях RhoA / ROCK. У той час як проліферація та міграція цих клітин, спровокована алкоголем, HNE (еластазою нейтрофілів людини), PDGF, IL-33 регулюється шляхами MAP-кінази і PI3K. Сигнальний шлях Wnt сприяє накопиченню колагену. Через шлях AMPK / mTOR фактор FTY720 індукує апоптоз та пригнічує аутофагію зірчастих панкреатоцитів. Взаємодія PSC і пухлинних клітин опосередковується також через Notch і TGF-β, а через сигнальний шлях Hippo за участю чинників YAP / TAZ можливо придушення фіброзної активності PSC. Взаємодія зірчастих панкреатоцитів і пухлинних клітин відбивається в прямій кореляції між зниженням аутофагії і апоптозу зірчастих панкреатоцитів і придушенням інвазії і міграції пухлинних клітин. Така взаємодія може забезпечуватись ERK1 / 2 кіназою. Серед чинників, що виділяються пухлинними клітинами і викликають активацію PSC відзначають: фактор росту β1 (TGF-β1), білок PAI-1, фактор ініціації трансляції 4E (eIF4E), sHH (залучає PSC в розгортання болю), екзосоми Exo-Pan і Exo-Mia (ангажують PSC в канцерогенез). Деактивація забезпечується медіаторним колоністимулюю-

чим фактором 1 (CSF1R, цитокин). У свою чергу зірчасті панкреатоцити виділяють хемокін CXCL1, стимулюючий міграцію та інвазію пухлинних клітин, екзосоми з безліччю miRNA, що стимулюють проліферацію, міграцію ракових клітин. **Підсумок**. Активація зірчастих панкреатоцитів, яка необхідна для реалізації їх фібротических функцій, забезпечується через сигнальний шлях RhoA / ROCK за допомогою серотоніну. У регуляції активності зірчастих панкреатоцитів задіяні також шлях Hippo (активація) і AMPK / mTOR (придушення аутофагії і активація апоптозу). Взаємодія між пухлинними клітинами і зірчастими панкреатоцитами здійснюється через сигнальні шляхи Hedgehog, Notch і TGF-β; регуляція інвазії і метастазування ракових клітин забезпечує сигнальний шлях HGF / c-Met / сурвівін.

Ключові слова: зірчасті панкреатоцити, пухлинні клітини підшлункової, мікрооточення пухлини, сигнальні шляхи, хіміорезистентність.

Станишевская Н.В. Сигнальные пути, которые вовлечены в активизацию звездчатых панкреатоцитив и взаимодействие с раковыми клетками поджелудочной железы.

РЕФЕРАТ. **Актуальность.** Активация, пролиферация и миграционные возможности звездчатых панкреатоцитов обеспечиваются рядом сигнальных молекулярных механизмов, поддерживающих взаимодействие опухолевых клеток с PSC и детерминирующих неопластический процесс. **Цель.** Обзор является продолжением серии статей, посвященных современному представлению о роли и функциях звездчатых панкреатоцитив, а именно их вовлечению во взаимодействие с раковыми клетками и сигнальными молекулярными путями, которые обеспечивают синергизм системы звездчатый панкреатоцит-раковая клетка. **Методы.** Обработка данных осуществлялась методом комплексного анализа материала. **Результаты.** Сигнальный путь Hedgehog обеспечивает взаимодействие PSC и опухолевых клеток, в котором задействован ведущий медиатор этого пути – sHH (sonic hedgehog), сверхэкспрессия которого регистрируется в опухолевой ткани поджелудочной железы и обеспечивает формирование стромы опухоли. Звездчатые панкреатоциты запускают также сигнальный путь HGF / c-Met / сурвивин, обеспечивающий инвазию и метастазирование. Активация самих PSC может быть опосредована серотонином через сигнальный путь RhoA / ROCK. В то время как пролиферация и миграция этих клеток, активизируемая алкоголем, HNE (эластазой нейтрофилов человека), PDGF, IL-33 PSC регулируются путями MAP-киназы и PI3K. Сигнальный путь Wnt способствует накапливанию коллагена. Через путь AMPK / mTOR фактор FTY720 индуцирует апоптоз и ингибирует аутофагию звездчатых панкреатоцитов. Взаимодействие PSC и опухолевых клеток опосредуется также через Notch и TGF-β, а через сигнальный путь Hippo при участии факторов YAP / TAZ возможно подавление фиброзной активности PSC. Взаимодействие звездчатых панкреатоцитов и опухолевых клеток отражается в прямой корреляции между снижением аутофагии и апоптоза звездчатых панкреатоцитов и подавлением инвазии и миграции опухолевых клеток. Такое взаимодействие может обеспечиваться ERK1 / 2 киназой. Среди факторов выделяемых опухолевыми клетками и вызывающих активацию PSC отмечают: фактор роста β1 (TGF-β1), белок PAI-1, фактор инициации трансляции 4E (eIF4E), sHH (вовлекающий PSC в развертывание боли), экзосомы Exo-Pan и Exo-Mia (ангажирующие PSC в канцерогенез). Деактивация обеспечивается медиаторным колониестимулирующим фактором 1 (CSF1R, цитокин). В свою очередь звездчатые панкреатоциты выделяют хемокин CXCL1, стимулирующий миграцию и инвазию опухолевых клеток, экзосомы с множеством miRNA, стимулирующие пролиферацию, миграцию раковых клеток. **Заключение.** Активация звездчатых панкреатоцитов, которая необходима для реализации их фибротических функций, обеспечивается через сигнальный путь RhoA / ROCK посредством серотонина. В регуляции активности звездчатых панкреатоцитов задействованы также путь Hippo (активация) и AMPK / mTOR (подавление аутофагии и активация апоптоза). Взаимодействие между опухолевой клеткой и звездчатым панкреатоцитом осуществляется через сигнальные пути Hedgehog, Notch и TGF-β; регуляция инвазии и метастазирования раковых клеток обеспечивает сигнальный путь HGF / c-Met / сурвивин.

Ключевые слова: звездчатые панкреатоциты, опухолевые клетки поджелудочной железы, микросреда опухоли, сигнальные пути, химиорезистентность.