BBA - Reviews on Cancer 1871 (2019) 267–272

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

Reflections on depletion of tumor stroma in pancreatic cancer☆

Wen-Quan Wang[a,b,c,d,1], Liang Liu[a,b,c,d,1], Jin-Zhi Xu[a,b,c,d], Xian-Jun Yu[a,b,c,d,*]

[a] Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China
[b] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China
[c] Shanghai Pancreatic Cancer Institute, Shanghai, China
[d] Pancreatic Cancer Institute, Fudan University, Shanghai, China

ARTICLE INFO

Keywords:
Pancreatic cancer
Stroma-targeting therapy
Metastasis
Cancer-associated fibroblasts

ABSTRACT

Pancreatic cancer characteristically has an extremely dense stroma, which facilitates chemoresistance by creating physical and biological barriers to therapeutic agents. Thus, stroma-depleting agents may enhance the delivery and efficacy of chemotherapy drugs. However, stroma-targeting therapy for pancreatic cancer is a double-edged sword, as the stroma can also inhibit tumor metastasis and malignancy. In-depth understanding of the critical role of the stroma in cancer metastasis may improve therapeutic approaches by allowing them to harness specific features of the stroma to treat pancreatic cancer.

1. Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths worldwide, with a 5-year survival rate of < 8% [1]. Surgical resection is the only potentially curative therapy for this highly lethal malignancy [2]. However, only 15–20% of pancreatic cancer patients are considered surgery candidates at the time of diagnosis [3]. Comprehensive chemotherapy-based treatment is the primary strategy for the remaining > 80% of patients with unresectable disease. Despite significant progress in the development of new chemotherapy regimens [4–8] over the past 20 years, the overall chemotherapeutic efficacy against pancreatic cancer remains low. Therefore, investigation of novel strategies is extremely important for improving pancreatic cancer outcomes. Certain molecular therapies, such as anti-angiogenic agents and epidermal growth factor receptor antagonists, have shown little to no benefit in patients with pancreatic cancer [9–11]. Specific biological mechanisms likely hinder the effectiveness of these therapies.

The highly heterogeneous pancreatic cancers are generally characterized by the presence of a dense stroma, with extensive fibroblasts proliferation and extracellular matrix (ECM) deposition [12]. The stroma can constitute in excess of 50% of the tumor volume, comprising cancer-associated fibroblasts (CAFs), blood vessels, hyaluronan, collagen fibers, infiltrating immune and inflammatory cells, nerve fibers, and adipocytes [12,13]. The de-differentiated tumor cells distributed throughout the stromal components with the immature adenoid structure, when compared with the mature pancreas cell types [12,14]. Within this environment, the intratumoral microvessels are highly compressed, limiting the uptake of chemotherapy agents. These properties create a physical and biochemical barrier that, when coupled with the complex tumor microenvironment and the biological resistance of pancreatic cancer cells to chemotherapy [15,16], results in poor response to most treatment options. Therefore, strategies to eliminate or remodel this physical and biochemical barrier could substantially improve chemotherapy delivery and efficacy.

2. Overview of stromal biology in pancreatic cancer

Stromal components modulate pancreatic cancer progression [12,17]. CAFs, among the most important constituents of the stroma, play a central role in malignant tumor behavior. They contribute to the establishment of an immunosuppressive tumor microenvironment, the secretion of cytokines that promote tumor growth, metastasis, and chemoresistance, and the induction of systemic effects, such as cachexia and acidosis [18–21]. Collagen fibers, another important stromal component, promote pancreatic cancer progression by signaling cancer cells to enhance growth, maintain a migratory phenotype, and avoid apoptosis, as well as by providing a basement-membrane-like architecture adjacent to the cancer cells and by enhancing tissue tension,

☆ Review

* Corresponding author at: Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center; Shanghai Pancreatic Cancer Institute; Pancreatic Cancer Institute, Fudan University, 270 Dong An Road, Shanghai 200032, China.

E-mail address: yuxianjun@fudanpci.org (X.-J. Yu).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.bbcan.2019.01.007
Received 14 October 2018; Received in revised form 21 January 2019; Accepted 22 January 2019
Available online 06 February 2019
0304-419X/

stromal hypoxia, and drug resistance [22–24]. High levels of specific fibrillar collagens adjacent to epithelial lesions are associated with poorly differentiated pancreatic cancer and reduced overall survival rates [24]. In addition, a variety of immune cells infiltrate the stromal niche, interact with stromal and cancer cells, and promote the growth and phenotype of this aggressive neoplasm [13,20,25]. Increasing numbers of studies have demonstrated that depletion or inactivation of these tumor-promoting stromal cells reduces the abundance of ECM proteins and inhibits growth and metastasis of desmoplastic human pancreatic cancer [17,18,26–29].

3. Investigations of stroma depletion in pancreatic cancer

Considering the role of the stroma in pancreatic cancer, the underlying pathways represents a target for restraining the malignant behavior. Six major mechanisms drive the generation of desmoplastic stroma: ECM remodeling by secreted protein acidic and rich in cysteine (SPARC) [30], tumor stroma depletion by CD40-activated tumor-associated macrophages [31], microvascular wall collapse derived from tumor endothelial cell damage by gamma-secretase activation in the Notch signaling pathway [32,33], microvascular structural and functional impairment from extensively deposited hyaluronan on the extracellular interstitium [34,35], pancreatic stellate cell (PSC)/CAF activation by Hedgehog signaling pathway stimulation [36,37], and Rho-associated protein kinase (ROCK)-induced extracellular collagen remodeling [38]. Although the comparative importance of these mechanisms has not been determined, they do not function in isolation. Under certain circumstances, they interact with each other and synergistically promote the stromal progression of pancreatic cancer [39]. Additional mechanisms may contribute to stromal development. For instance, intratumorally infiltrated nerve fibers may regulate CAFs, termed neuronal CAFs, with potential common regulatory targets [40]. Elucidating the intrinsic connections between these mechanisms and identifying the key regulatory targets can pave the way for clinical investigations of strategies to deplete the stroma in pancreatic cancer patients.

Theoretically, targeting any of these pathways may suppress the stromal progression of pancreatic cancer. A SPARC-targeting agent [41], a CD40 agonist [31], a gamma-secretase inhibitor (Notch signaling inhibitor) [33,42], a human recombinant hyaluronidase [35], a Hedgehog pathway inhibitor [36], and a ROCK small-molecule inhibitor [38,43] have all been shown to trigger tumor stroma ablation in genetically engineered mouse models of pancreatic cancer, restoring the structure and function of tumor microvessels. Consequently, these compounds substantially increased perfusion, diffusion, and convection of small-molecule therapeutics, thus representing good prospects for clinical development.

4. Clinical exploration of stroma-depleting agents

Preclinical studies have highlighted the prospect of utilizing stroma-targeting treatments (Fig. 1), paving the road for several clinical trials examining the use of stroma-depleting agents in pancreatic cancer (Table 1). However, most of these agents did not successfully translate into clinical use. Although the SPARC-targeting chemotherapy drug nab-paclitaxel successfully achieved clinical translation [6,44], later studies demonstrated that its efficacy does not depend on SPARC expression and, thus, stromal depletion [45–47]. Furthermore, tumor growth and metastasis may tend to accelerate following the development of nab-paclitaxel resistance [48]. To date, this phenomenon, combined with the differential response between primary and metastatic tumor lesions, has not yet attracted enough attention from gastroenteropancreatic oncologists.

Among the other therapeutic agents, both the Hedgehog pathway inhibitor vismodegib [49,50] and the CD40 agonist CP-870,893 (NCT02304393) have not exhibited a clear survival benefit in clinical research. Even worse, another Hedgehog pathway inhibitor IPI-926 [51,52] (ClinicalTrials.gov, NCT01130142) showed a clear adverse effect. Recently, the PEGylated recombinant human hyaluronidase PEGPH20 has shown some promising potential benefits in both preclinical [34,35] and preliminary clinical studies [53] (NCT01453153, NCT01839487, NCT02715804). However, its use and efficacy remain controversial because of some detrimental effects reported in a recent clinical study [54] (NCT01959139).

Facilitated by research investigating the stromal microenvironment of pancreatic cancer, stroma-depleting approaches have the potential to revolutionize cancer care. However, they remain a long way from regular and robust clinical application.

5. Causes and prevention of negative effects of stromal depletion

Most mechanistic studies have concluded that the desmoplastic stroma of pancreatic ductal adenocarcinoma (PDAC) plays an essential role in maintaining the malignant biological behavior of the tumor cells [12,25,38]. However, combinations of stromal depletion strategies and systemic chemotherapy have not benefited patients in clinical studies (Table 1) [49–52,54], indicating that PDAC stroma likely possess protective biological features. Ozdemir et al. [55], Rhim et al. [56], and Lee et al. [57] independently verified that ablation of myofibroblasts or CAFs in PDAC, through inhibition of the Hedgehog signaling pathway or depletion of the α-smooth muscle actin $(SMA)^+$ CAFs accelerates metastatic processes and reduces survival in a mouse model of pancreatic cancer. In addition, in these studies, the tumor cells exhibited loss of differentiation at the primary sites, an epithelial-to-mesenchymal transition, and an enhanced cancer stem cell-like phenotype. Increased immunosuppression, hypoxia, and vascular density, together with loss of vascular integrity, were observed in the stromal niches. Furthermore, the PDAC mice suffered severe weight loss, acidosis, and cachexia [55–58]. Anti-angiogenic agents [56] and anti-CTLA4 immunotherapy [55] could partially reverse disease acceleration and prolong survival in mice. We have previously shown an association between elevated $\alpha\text{-SMA}^+$ myofibroblast and $CD34^+$ vascular endothelial cell levels in tumors, indicative of enhanced microvessel integrity, and improved survival rates following curative resection [59]. Taken together, these findings suggest that the negative effects of stromal depletion in pancreatic cancer potentially occur *via* activation of dormant tumor cells and induction of the metastatic potential, resulting in the presence of chemotherapy-resistant residual tumor cells that are transported to distant organs through incomplete microvessels.

Various CAF subpopulations, exhibiting distinct properties and activation levels, have been recently detected in breast [60] and pancreatic cancers [61]. These heterogeneous CAF populations potentially contain previously unidentified distinct subsets of microvessel-associated CAFs (mvaCAFs) (Fig. 1). Indiscriminate depletion of CAFs is likely to harm favourable CAF subsets, compromising microvessel integrity and accelerating metastasis. Platelet-derived growth factor receptor-β (PDGFR-β), a major biomarker and functional molecule associated with vascular pericytes [62], is strongly expressed in $\alpha\text{-SMA}^+$ myofibroblasts [59,60]. The relationship between pericyte- and mvaCAF-derived PDGFR-β has not been investigated, and the question of whether pericytes and mvaCAFs represent the same cell type remains unanswered. However, one study has revealed that therapies that antagonize PDGFR-β (*i.e.*, imatinib and sunitinib) also lead to decoupling of pericyte-endothelial cells, thus reducing microvessel integrity and promoting metastasis [62]. This unique perspective proposes that the depletion of the stroma in pancreatic cancer has a negative effect and promotes metastasis. Although desmoplastic stroma-targeting therapies can enhance the delivery of chemotherapeutic agents, they can also result in the presence of resistant tumor cells. Thus, the opening of vessel channels can subsequently lead to increased tumor metastasis.

Therefore, strategies to suppress the negative effects of stromal depletion strategies are key to improving the efficacy of these

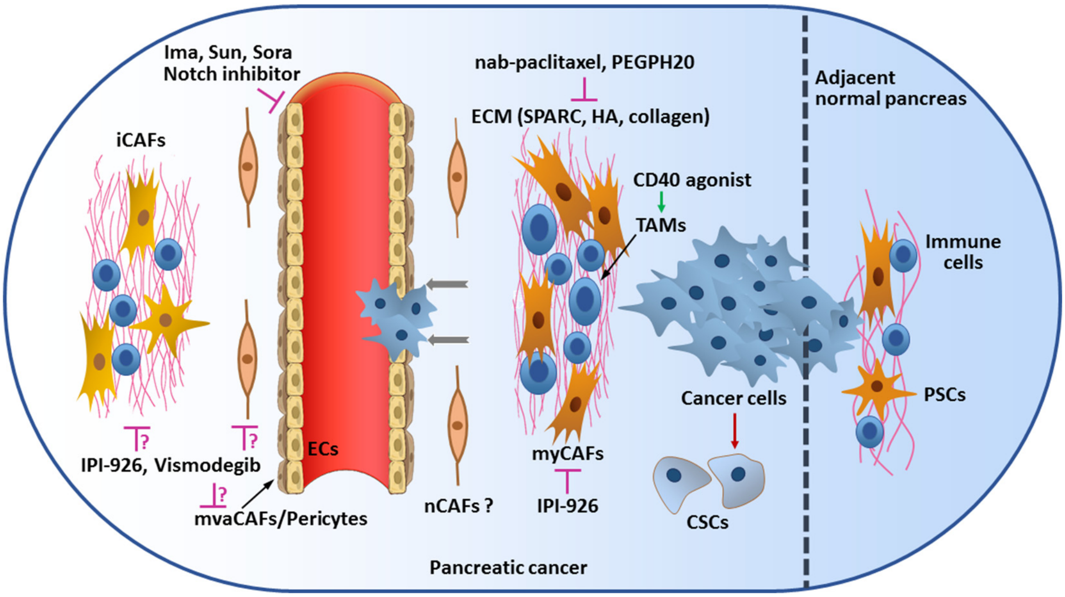

Fig. 1. Schematic of the interstitial network and stromal depletion mechanisms in pancreatic cancer. Cancer-associated fibroblasts (CAFs) comprise multiple subtypes, including inflammatory CAFs (iCAFs), myofibroblastic CAFs (myCAFs), microvessel-associated CAFs (mvaCAFs)/pericytes, and neuronal CAFs (nCAFs), as well as other unidentified subtypes. CAFs and pancreatic stellate cells (PSCs) demonstrate a certain degree of similarity. Depletion of CAFs and fibrosis by Hedgehog pathway inhibitors (IPI-926 and vismodegib) or CD40 agonists undermines microvessel integrity, leading to invasive undifferentiated tumors with enhanced hypoxia and increased numbers of cancer stem cells (CSCs). Targeting of other CAFs, such as iCAFs, mvaCAFs, and nCAFs, by Hedgehog inhibitors remains to be investigated. Pink T-mark represents inhibition; green arrow, activation; black arrow, indication; red arrow, direction of differentiation; gray arrow, invasion; question mark, relationship remains to be verified. Abbreviations: ECM, extracellular matrix; ECs, endothelial cells; HA, hyaluronic acid; SPARC, the secreted protein acid and rich in cysteine; TAMs, tumor-associated macrophages; Ima, imatinib; Sun, sunitinib; Sora, sorafenib.

therapeutic interventions. Approaches enhancing tumor microvessel integrity, antagonizing neovascular formation, and transforming the malignant metastatic potential of tumor cells may increase the clinical efficacy of desmoplastic stroma-targeting therapies, thereby prolonging the survival of pancreatic cancer patients receiving chemotherapy. Approaches to precisely identify and eliminate or transform the pathogenic CAF cells into protective or beneficial subsets [60,61,63,64] through genomic analyses and genetic engineering methods [65,66] represent another valuable avenue for future research.

6. Discussion, reflection, and perspective

Clinical studies have not demonstrated that stromal depletion can lead to acceleration of tumor progression and metastasis. However, preclinical studies linking the underlying mechanisms with metastasis (Fig. 1) warn against the implementation of such therapeutic approaches. Notably, different stromal depletion treatment strategies may have mechanism-specific negative outcomes, requiring distinct clinical approaches. Even in the same patient, inherent heterogeneity of the stromal microenvironment in primary tumors and metastatic foci may result in different negative effects, mainly displaying as the primary tumor shrinks and the metastases increase, or *vice versa*. In addition, the effects of individual- and ethnic-group-specific genetic variations on the stromal microenvironment of pancreatic cancer remain to be investigated. Genomic analyses of between- and within-individual heterogeneity of the stromal niche [64–66] can facilitate optimized and personalized stroma-targeting treatment and prevention strategies based on specific tumor characteristics, thereby minimizing negative outcomes.

Prevention of negative effects can be facilitated by drugs that promote the normalization of microvessels [67]. These substances can promote the integrity of microvascular structure and function and, consequently, repress tumor cell intravasation and invasion of microvessels, as well as improve chemotherapy drug uptake. They can also prevent tumor cells from colonizing target organs and promote their apoptosis in blood circulation, thereby inhibiting metastasis and enhancing chemotherapeutic efficacy. In addition, some drugs that modify the tumor stromal microenvironment can also exhibit synergistic effects. For example, pharmacological depletion of tumor-associated macrophages and inhibition of downstream signaling by liposomal clodronate prevents the establishment of a pre-metastatic microenvironment in target organs, thereby markedly reducing metastasis formation [68]. Thus, liposomal clodronate represents a candidate for combination strategies with stroma-targeting therapies.

Table 1
Summary of clinical studies involving stroma-depleting agents in pancreatic cancer.

Agents	mPFS (95% CI, months)	mOS (95% CI, months)	Progressive Pattern	Reference
Nab-paclitaxel	1.7 (1.5–3.5)	7.3 (2.8–15.8)	No description	2013 [47]
Nab-paclitaxel + gem *vs. gem*	5.5 (4.5–5.9) *vs.* 3.7 (3.6–4.0)	8.5 (7.9–9.5) *vs.* 6.7 (6.0–7.2)	No description	2013 [6], 2015 [44]
FOLFIRINOX + IPI-926	8.4	No description	No description	2016 [51]
Gem + IPI-926 *vs.* gem	The former < the latter	The former < the latter	No description	2012 [52]
Gem + vismodegib	2.8 (1.4–4.7)	5.3 (3.6–8.4)	No description	2014 [49]
Gem + vismodegib *vs.* gem	4.0 (2.5–5.3) *vs.* 2.5 (1.9–3.8)	6.9 (5.8–8.0) *vs.* 6.1 (5.0–8.0)	No description	2015 [50]
Gem + PEGPH20	5.0 (1.6–5.4)	6.6 (4.0–12.1)	No description	2016 [53]
FOLFIRINOX + PEGPH20 *vs.* FOLFIRINOX	4.3 *vs.* 6.2	7.7 *vs.* 14.4	No description	2018 [54]

Abbreviations: mPFS, median progression-free survival; mOS, median overall survival; CI, confidence interval; Gem, gemcitabine.

An exploratory analysis conducted in the phase 3 metastatic pancreatic adenocarcinoma clinical trial underscored the benefit of nab-paclitaxel plus gemcitabine against both primary pancreatic and metastatic lesions [69]. However, differential responses between primary tumor and metastatic foci are increasingly being observed in clinical practice, with no references available to date. While the primary tumor is under control, the metastatic foci may continue to grow. Therefore, considering the potential pro-metastatic effects of stroma depletion, this regimen may not be preferable for preoperative neoadjuvant therapy in patients with locally advanced pancreatic cancer. Finally, although stromal progression is often accompanied by enhanced immunosuppression in PDAC [64], as depletion of stroma may also exacerbate PDAC immunosuppression under certain circumstances [55], the tumor cells may be more susceptible to immune escape and, thus, more prone to metastasis. Therefore, under the premise that adverse reactions are controllable, combining regiments with immune checkpoint inhibitors (*e.g.*, anti-PD-1/PD-L1 [70] or anti-CTLA4 [55]) can potentially reduce the negative effects of stroma-targeting treatment and further enhance the anti-tumor efficacy of chemotherapy.

In summary, therapeutic regimens targeting the pancreatic cancer stroma represent a double-edged sword. They can increase the perfusion of chemotherapeutic drugs to the tumor, but also ablate the physical and biochemical barriers preventing tumor metastasis. The latter effect can lead to a series of negative events compromising chemo-efficacy. In-depth understanding of the role of the stroma can improve therapeutic strategies by allowing them to modify and harness the stromal niche in pancreatic cancer toward effectively inhibiting malignant cancer growth without inducing tumor metastasis.

Financial support

This work was supported by grants from the National Science Foundation for Distinguished Young Scholars of China (81625016), the National Natural Science Foundation of China (81872366, 81472670, 81871941, 81802380, and 81802675), the Outstanding Academic Leader Program of the Technological Innovation Action Plan of the Shanghai Science and Technology Commission (18XD1401200), and the Young Talented Specialist Training Program of Shanghai.

Conflict of interest

The authors declare no conflicts of interest.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (2018) 7–30.
[2] D.P. Ryan, T.S. Hong, N. Bardeesy, Pancreatic adenocarcinoma, N. Engl. J. Med. 371 (2014) 1039–1049.
[3] T. Kamisawa, L.D. Wood, T. Itoi, K. Takaori, Pancreatic cancer, Lancet 388 (2016) 73–85.
[4] H.A. Burris 3rd, M.J. Moore, J. Andersen, M.R. Green, M.L. Rothenberg, M.R. Modiano, M.C. Cripps, R.K. Portenoy, A.M. Storniolo, P. Tarassoff, R. Nelson, F.A. Dorr, C.D. Stephens, D.D. Von Hoff, Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial, J. Clin. Oncol. 15 (1997) 2403–2413.
[5] T. Conroy, F. Desseigne, M. Ychou, O. Bouche, R. Guimbaud, Y. Becouarn, A. Adenis, J.L. Raoul, S. Gourgou-Bourgade, C. de la Fouchardiere, J. Bennouna, J.B. Bachet, F. Khemissa-Akouz, D. Pere-Verge, C. Delbaldo, E. Assenat, B. Chauffert, P. Michel, C. Montoto-Grillot, M. Ducreux, U. Groupe Tumeurs Digestives of, P. Intergroup, FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, N. Engl. J. Med. 364 (2011) (1817-1825).
[6] D.D. Von Hoff, T. Ervin, F.P. Arena, E.G. Chiorean, J. Infante, M. Moore, T. Seay, S.A. Tjulandin, W.W. Ma, M.N. Saleh, M. Harris, M. Reni, S. Dowden, D. Laheru, N. Bahary, R.K. Ramanathan, J. Tabernero, M. Hidalgo, D. Goldstein, E. Van Cutsem, X. Wei, J. Iglesias, M.F. Renschler, Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine, N. Engl. J. Med. 369 (2013) 1691–1703.
[7] A. Wang-Gillam, C.P. Li, G. Bodoky, A. Dean, Y.S. Shan, G. Jameson, T. Macarulla, K.H. Lee, D. Cunningham, J.F. Blanc, R.A. Hubner, C.F. Chiu, G. Schwartsmann, J.T. Siveke, F. Braiteh, V. Moyo, B. Belanger, N. Dhindsa, E. Bayever, D.D. Von Hoff, L.T. Chen, N.-S. Group, Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial, Lancet 387 (2016) 545–557.
[8] V. Heinemann, U. Vehling-Kaiser, D. Waldschmidt, E. Kettner, A. Marten, C. Winkelmann, S. Klein, G. Kojouharoff, T.C. Gauler, L.F. von Weikersthal, M.R. Clemens, M. Geissler, T.F. Greten, S. Hegewisch-Becker, O. Rubanov, G. Baake, T. Hohler, Y.D. Ko, A. Jung, S. Neugebauer, S. Boeck, Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104), Gut 62 (2013) 751–759.
[9] K.E. Craven, J. Gore, M. Korc, Overview of pre-clinical and clinical studies targeting angiogenesis in pancreatic ductal adenocarcinoma, Cancer Lett. 381 (2016) 201–210.
[10] M.J. Moore, D. Goldstein, J. Hamm, A. Figer, J.R. Hecht, S. Gallinger, H.J. Au, P. Murawa, D. Walde, R.A. Wolff, D. Campos, R. Lim, K. Ding, G. Clark, T. Voskoglou-Nomikos, M. Ptasynski, W. Parulekar, G. National Cancer Institute of Canada Clinical Trials, Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group, J. Clin. Oncol. 25 (2007) (1960-1966).
[11] M. Sinn, M. Bahra, T. Liersch, K. Gellert, H. Messmann, W. Bechstein, D. Waldschmidt, L. Jacobasch, M. Wilhelm, B.M. Rau, R. Grutzmann, A. Weinmann, G. Maschmeyer, U. Pelzer, J.M. Stieler, J.K. Striefler, M. Ghadimi, S. Bischoff, B. Dorken, H. Oettle, H. Riess, CONKO-005: adjuvant chemotherapy with gemcitabine plus erlotinib versus gemcitabine alone in patients after R0 resection of pancreatic cancer: a multicenter randomized phase III trial, J. Clin. Oncol. 35 (2017) 3330–3337.
[12] C. Feig, A. Gopinathan, A. Neesse, D.S. Chan, N. Cook, D.A. Tuveson, The pancreas cancer microenvironment, Clin. Cancer Res. 18 (2012) 4266–4276.
[13] W.Q. Wang, L. Liu, H.X. Xu, C.T. Wu, J.F. Xiang, J. Xu, C. Liu, J. Long, Q.X. Ni, X.J. Yu, Infiltrating immune cells and gene mutations in pancreatic ductal adenocarcinoma, Br. J. Surg. 103 (2016) 1189–1199.
[14] B.Z. Stanger, M. Hebrok, Control of cell identity in pancreas development and regeneration, Gastroenterology 144 (2013) 1170–1179.
[15] A. Rajabpour, F. Rajaei, L. Teimoori-Toolabi, Molecular alterations contributing to pancreatic cancer chemoresistance, Pancreatology 17 (2017) 310–320.
[16] P. Dauer, A. Nomura, A. Saluja, S. Banerjee, Microenvironment in determining chemo-resistance in pancreatic cancer: Neighborhood matters, Pancreatology 17 (2017) 7–12.
[17] A. Neesse, P. Michl, K.K. Frese, C. Feig, N. Cook, M.A. Jacobetz, M.P. Lolkema, M. Buchholz, K.P. Olive, T.M. Gress, D.A. Tuveson, Stromal biology and therapy in pancreatic cancer, Gut 60 (2011) 861–868.
[18] M.H. Sherman, R.T. Yu, T.W. Tseng, C.M. Sousa, S. Liu, M.L. Truitt, N. He, N. Ding, C. Liddle, A.R. Atkins, M. Leblanc, E.A. Collisson, J.M. Asara, A.C. Kimmelman, M. Downes, R.M. Evans, Stromal cues regulate the pancreatic cancer epigenome and metabolome, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 1129–1134.
[19] M. Waghray, M. Yalamanchili, M. Dziubinski, M. Zeinali, M. Erkkinen, H. Yang, K.A. Schradle, S. Urs, M. Pasca Di Magliano, T.H. Welling, P.L. Palmbos, E.V. Abel, V. Sahai, S. Nagrath, L. Wang, D.M. Simeone, GM-CSF mediates mesenchymal-epithelial cross-talk in pancreatic cancer, Cancer Discov. 6 (2016) 886–899.
[20] E. Pure, A. Lo, Can targeting stroma pave the way to enhanced antitumor immunity and immunotherapy of solid tumors? Cancer Immunol. Res. 4 (2016) 269–278.
[21] C.M. Sousa, D.E. Biancur, X. Wang, C.J. Halbrook, M.H. Sherman, L. Zhang, D. Kremer, R.F. Hwang, A.K. Witkiewicz, H. Ying, J.M. Asara, R.M. Evans, L.C. Cantley, C.A. Lyssiotis, A.C. Kimmelman, Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion, Nature 536 (2016) 479–483.
[22] D. Ohlund, O. Franklin, E. Lundberg, C. Lundin, M. Sund, Type IV collagen stimulates pancreatic cancer cell proliferation, migration, and inhibits apoptosis through an autocrine loop, BMC Cancer 13 (2013) 154.
[23] S. Berchtold, B. Grunwald, A. Kruger, A. Reithmeier, T. Hahl, T. Cheng, A. Feuchtinger, D. Born, M. Erkan, J. Kleeff, I. Esposito, Collagen type V promotes the malignant phenotype of pancreatic ductal adenocarcinoma, Cancer Lett. 356 (2015) 721–732.
[24] H. Laklai, Y.A. Miroshnikova, M.W. Pickup, E.A. Collisson, G.E. Kim, A.S. Barrett, R.C. Hill, J.N. Lakins, D.D. Schlaepfer, J.K. Mouw, V.S. LeBleu, N. Roy, S.V. Novitskiy, J.S. Johansen, V. Poli, R. Kalluri, C.A. Iacobuzio-Donahue, L.D. Wood, M. Hebrok, K. Hansen, H.L. Moses, V.M. Weaver, Genotype tunes pancreatic ductal adenocarcinoma tissue tension to induce matricellular fibrosis and tumor progression, Nat. Med. 22 (2016) 497–505.
[25] M.F. Nielsen, M.B. Mortensen, S. Detlefsen, Key players in pancreatic cancer-stroma interaction: cancer-associated fibroblasts, endothelial and inflammatory cells, World J. Gastroenterol. 22 (2016) 2678–2700.
[26] A. Lo, L.S. Wang, J. Scholler, J. Monslow, D. Avery, K. Newick, S. O'Brien, R.A. Evans, D.J. Bajor, C. Clendenin, A.C. Durham, E.L. Buza, R.H. Vonderheide, C.H. June, S.M. Albelda, E. Pure, Tumor-promoting desmoplasia is disrupted by depleting FAP-expressing stromal cells, Cancer Res. 75 (2015) 2800–2810.
[27] G.L. Beatty, R. Winograd, R.A. Evans, K.B. Long, S.L. Luque, J.W. Lee, C. Clendenin, W.L. Gladney, D.M. Knoblock, P.D. Guirnalda, R.H. Vonderheide, Exclusion of T cells from pancreatic carcinomas in mice is regulated by Ly6C(low) F4/80(+) extratumoral macrophages, Gastroenterology 149 (2015) 201–210.
[28] D.T. Fearon, The carcinoma-associated fibroblast expressing fibroblast activation protein and escape from immune surveillance, Cancer Immunol. Res. 2 (2014) 187–193.
[29] C. Feig, J.O. Jones, M. Kraman, R.J. Wells, A. Deonarine, D.S. Chan, C.M. Connell, E.W. Roberts, Q. Zhao, O.L. Caballero, S.A. Teichmann, T. Janowitz, D.I. Jodrell, D.A. Tuveson, D.T. Fearon, Targeting CXCL12 from FAP-expressing carcinoma-

associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 20212–20217.
[30] C. Neuzillet, A. Tijeras-Raballand, J. Cros, S. Faivre, P. Hammel, E. Raymond, Stromal expression of SPARC in pancreatic adenocarcinoma, Cancer Metastasis Rev. 32 (2013) 585–602.
[31] G.L. Beatty, E.G. Chiorean, M.P. Fishman, B. Saboury, U.R. Teitelbaum, W. Sun, R.D. Huhn, W. Song, D. Li, L.L. Sharp, D.A. Torigian, P.J. O'Dwyer, R.H. Vonderheide, CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans, Science 331 (2011) 1612–1616.
[32] R. Plentz, J.S. Park, A.D. Rhim, D. Abravanel, A.F. Hezel, S.V. Sharma, S. Gurumurthy, V. Deshpande, C. Kenific, J. Settleman, P.K. Majumder, B.Z. Stanger, N. Bardeesy, Inhibition of gamma-secretase activity inhibits tumor progression in a mouse model of pancreatic ductal adenocarcinoma, Gastroenterology 136 (2009) 1741–1749 (e1746).
[33] N. Cook, K.K. Frese, T.E. Bapiro, M.A. Jacobetz, A. Gopinathan, J.L. Miller, S.S. Rao, T. Demuth, W.J. Howat, D.I. Jodrell, D.A. Tuveson, Gamma secretase inhibition promotes hypoxic necrosis in mouse pancreatic ductal adenocarcinoma, J. Exp. Med. 209 (2012) 437–444.
[34] P.P. Provenzano, C. Cuevas, A.E. Chang, V.K. Goel, D.D. Von Hoff, S.R. Hingorani, Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma, Cancer Cell 21 (2012) 418–429.
[35] M.A. Jacobetz, D.S. Chan, A. Neesse, T.E. Bapiro, N. Cook, K.K. Frese, C. Feig, T. Nakagawa, M.E. Caldwell, H.I. Zecchini, M.P. Lolkema, P. Jiang, A. Kultti, C.B. Thompson, D.C. Maneval, D.I. Jodrell, G.I. Frost, H.M. Shepard, J.N. Skepper, D.A. Tuveson, Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer, Gut 62 (2013) 112–120.
[36] K.P. Olive, M.A. Jacobetz, C.J. Davidson, A. Gopinathan, D. McIntyre, D. Honess, B. Madhu, M.A. Goldgraben, M.E. Caldwell, D. Allard, K.K. Frese, G. Denicola, C. Feig, C. Combs, S.P. Winter, H. Ireland-Zecchini, S. Reichelt, W.J. Howat, A. Chang, M. Dhara, L. Wang, F. Ruckert, R. Grutzmann, C. Pilarsky, K. Izeradjene, S.R. Hingorani, P. Huang, S.E. Davies, W. Plunkett, M. Egorin, R.H. Hruban, N. Whitebread, K. McGovern, J. Adams, C. Iacobuzio-Donahue, J. Griffiths, D.A. Tuveson, Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer, Science 324 (2009) 1457–1461.
[37] M. Hidalgo, A. Maitra, The hedgehog pathway and pancreatic cancer, N. Engl. J. Med. 361 (2009) 2094–2096.
[38] N. Rath, J.P. Morton, L. Julian, L. Helbig, S. Kadir, E.J. McGhee, K.I. Anderson, G. Kalna, M. Mullin, A.V. Pinho, I. Rooman, M.S. Samuel, M.F. Olson, ROCK signaling promotes collagen remodeling to facilitate invasive pancreatic ductal adenocarcinoma tumor cell growth, EMBO Mol. Med. 9 (2017) 198–218.
[39] J.P.T. Morris, S.C. Wang, M. Hebrok, KRAS, Hedgehog, Wnt and the twisted developmental biology of pancreatic ductal adenocarcinoma, Nat. Rev. Cancer 10 (2010) 683–695.
[40] M.V. Apte, J.S. Wilson, A. Lugea, S.J. Pandol, A starring role for stellate cells in the pancreatic cancer microenvironment, Gastroenterology 144 (2013) 1210–1219.
[41] D.D. Von Hoff, R.K. Ramanathan, M.J. Borad, D.A. Laheru, L.S. Smith, T.E. Wood, R.L. Korn, N. Desai, V. Trieu, J.L. Iglesias, H. Zhang, P. Soon-Shiong, T. Shi, N.V. Rajeshkumar, A. Maitra, M. Hidalgo, Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial, J. Clin. Oncol. 29 (2011) 4548–4554.
[42] M. Mizuma, Z.A. Rasheed, S. Yabuuchi, N. Omura, N.R. Campbell, R.F. de Wilde, E. De Oliveira, Q. Zhang, O. Puig, W. Matsui, M. Hidalgo, A. Maitra, N.V. Rajeshkumar, The gamma secretase inhibitor MRK-003 attenuates pancreatic cancer growth in preclinical models, Mol. Cancer Ther. 11 (2012) 1999–2009.
[43] C. Vennin, V.T. Chin, S.C. Warren, M.C. Lucas, D. Herrmann, A. Magenau, P. Melenec, S.N. Walters, G. Del Monte-Nieto, J.R. Conway, M. Nobis, A.H. Allam, R.A. McCloy, N. Currey, M. Pinese, A. Boulghourjian, A. Zaratzian, A.A. Adam, C. Heu, A.M. Nagrial, A. Chou, A. Steinmann, A. Drury, D. Froio, M. Giry-Laterriere, N.L. Harris, T. Phan, R. Jain, W. Weninger, E.J. McGhee, R. Whan, A.L. Johns, J.S. Samra, L. Chantrill, A.J. Gill, M. Kohonen-Corish, R.P. Harvey, A.V. Biankin, I. Australian Pancreatic Cancer Genome, T.R. Evans, K.I. Anderson, S.T. Grey, C.J. Ormandy, D. Gallego-Ortega, Y. Wang, M.S. Samuel, O.J. Sansom, A. Burgess, T.R. Cox, J.P. Morton, M. Pajic, P. Timpson, Transient tissue priming via ROCK inhibition uncouples pancreatic cancer progression, sensitivity to chemotherapy, and metastasis, Sci. Transl. Med. 9 (2017).
[44] D. Goldstein, R.H. El-Maraghi, P. Hammel, V. Heinemann, V. Kunzmann, J. Sastre, W. Scheithauer, S. Siena, J. Tabernero, L. Teixeira, G. Tortora, J.L. Van Laethem, R. Young, D.N. Penenberg, B. Lu, A. Romano, D.D. Von Hoff, nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial, J. Natl. Cancer Inst. 107 (2015).
[45] A. Neesse, K.K. Frese, D.S. Chan, T.E. Bapiro, W.J. Howat, F.M. Richards, V. Ellenrieder, D.I. Jodrell, D.A. Tuveson, SPARC independent drug delivery and antitumour effects of nab-paclitaxel in genetically engineered mice, Gut 63 (2014) 974–983.
[46] M. Hidalgo, C. Plaza, M. Musteanu, P. Illei, C.B. Brachmann, C. Heise, D. Pierce, P.P. Lopez-Casas, C. Menendez, J. Tabernero, A. Romano, X. Wei, F. Lopez-Rios, D.D. Von Hoff, SPARC expression did not predict efficacy of nab-paclitaxel plus gemcitabine or gemcitabine alone for metastatic pancreatic cancer in an exploratory analysis of the phase III MPACT trial, Clin. Cancer Res. 21 (2015) 4811–4818.
[47] P.J. Hosein, G. de Lima Lopes Jr., V.H. Pastorini, C. Gomez, J. Macintyre, G. Zayas, I. Reis, A.J. Montero, J.R. Merchan, C.M. Rocha Lima, A phase II trial of nab-Paclitaxel as second-line therapy in patients with advanced pancreatic cancer, Am. J. Clin. Oncol. 36 (2013) 151–156.
[48] G. Giordano, M. Pancione, N. Olivieri, P. Parcesepe, M. Velocci, T. Di Raimo, L. Coppola, G. Toffoli, M.R. D'Andrea, Nano albumin bound-paclitaxel in pancreatic cancer: current evidences and future directions, World J. Gastroenterol. 23 (2017) 5875–5886.
[49] E.J. Kim, V. Sahai, E.V. Abel, K.A. Griffith, J.K. Greenson, N. Takebe, G.N. Khan, J.L. Blau, R. Craig, U.G. Balis, M.M. Zalupski, D.M. Simeone, Pilot clinical trial of hedgehog pathway inhibitor GDC-0449 (vismodegib) in combination with gemcitabine in patients with metastatic pancreatic adenocarcinoma, Clin. Cancer Res. 20 (2014) 5937–5945.
[50] D.V. Catenacci, M.R. Junttila, T. Karrison, N. Bahary, M.N. Horiba, S.R. Nattam, R. Marsh, J. Wallace, M. Kozloff, L. Rajdev, D. Cohen, J. Wade, B. Sleckman, H.J. Lenz, P. Stiff, P. Kumar, P. Xu, L. Henderson, N. Takebe, R. Salgia, X. Wang, W.M. Stadler, F.J. de Sauvage, H.L. Kindler, Randomized phase Ib/II study of gemcitabine plus placebo or Vismodegib, a Hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer, J. Clin. Oncol. 33 (2015) 4284–4292.
[51] A.H. Ko, N. LoConte, M.A. Tempero, E.J. Walker, R. Kate Kelley, S. Lewis, W.C. Chang, E. Kantoff, M.W. Vannier, D.V. Catenacci, A.P. Venook, H.L. Kindler, A phase I study of FOLFIRINOX plus IPI-926, a hedgehog pathway inhibitor, for advanced pancreatic adenocarcinoma, Pancreas 45 (2016) 370–375.
[52] J.I. Madden, Infinity reports update from phase 2 study of saridegib plus gemcitabine in patients with metastatic pancreatic cancer, Infinity Pharmaceut. (2012) Available at: http://www.businesswire.com/news/home/20120127005146/en/Infinity-Reports-Update-Phase-2-Study-Saridegib#.Vg2sAuGJMQM.
[53] S.R. Hingorani, W.P. Harris, J.T. Beck, B.A. Berdov, S.A. Wagner, E.M. Pshevlotsky, S.A. Tjulandin, O.A. Gladkov, R.F. Holcombe, R. Korn, N. Raghunand, S. Dychter, P. Jiang, H.M. Shepard, C.E. Devoe, Phase Ib study of PEGylated recombinant human hyaluronidase and gemcitabine in patients with advanced pancreatic cancer, Clin. Cancer Res. 22 (2016) 2848–2854.
[54] R.K. Ramanathan, S. McDonough, P.A. Philip, S.R. Hingorani, J. Lacy, J.S. Kortmansky, J.R. Thumar, E.G. Chiorean, A.F. Shields, D. Behl, P.T. Mehan, R. Gaur, T.E. Seery, K. Guthrie, H.S. Hochster, S1313, A Phase IB/II Randomized Study of Modified FOLFIRINOX + Pegylated Recombinant Human Hyaluronidase (PEGPH20) Versus Modified FOLFIRINOX Alone in Patients With Good Performance Status Metastatic Pancreatic Adenocarcinoma [Abstract 208], J. Clin. Oncol. (2018) ASCO-GI (suppl).
[55] B.C. Ozdemir, T. Pentcheva-Hoang, J.L. Carstens, X. Zheng, C.C. Wu, T.R. Simpson, H. Laklai, H. Sugimoto, C. Kahlert, S.V. Novitskiy, A. De Jesus-Acosta, P. Sharma, P. Heidari, U. Mahmood, L. Chin, H.L. Moses, V.M. Weaver, A. Maitra, J.P. Allison, V.S. LeBleu, R. Kalluri, Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival, Cancer Cell 25 (2014) 719–734.
[56] A.D. Rhim, P.E. Oberstein, D.H. Thomas, E.T. Mirek, C.F. Palermo, S.A. Sastra, E.N. Dekleva, T. Saunders, C.P. Becerra, I.W. Tattersall, C.B. Westphalen, J. Kitajewski, M.G. Fernandez-Barrena, M.E. Fernandez-Zapico, C. Iacobuzio-Donahue, K.P. Olive, B.Z. Stanger, Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma, Cancer Cell 25 (2014) 735–747.
[57] J.J. Lee, R.M. Perera, H. Wang, D.C. Wu, X.S. Liu, S. Han, J. Fitamant, P.D. Jones, K.S. Ghanta, S. Kawano, J.M. Nagle, V. Deshpande, Y. Boucher, T. Kato, J.K. Chen, J.K. Willmann, N. Bardeesy, P.A. Beachy, Stromal response to Hedgehog signaling restrains pancreatic cancer progression, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) E3091–E3100.
[58] K.J. Roberts, A.M. Kershner, P.A. Beachy, The stromal niche for epithelial stem cells: a template for regeneration and a brake on malignancy, Cancer Cell 32 (2017) 404–410.
[59] W.Q. Wang, L. Liu, H.X. Xu, G.P. Luo, T. Chen, C.T. Wu, Y.F. Xu, J. Xu, C. Liu, B. Zhang, J. Long, Z.Y. Tang, X.J. Yu, Intratumoral alpha-SMA enhances the prognostic potency of CD34 associated with maintenance of microvessel integrity in hepatocellular carcinoma and pancreatic cancer, PLoS One 8 (2013) e71189.
[60] A. Costa, Y. Kieffer, A. Scholer-Dahirel, F. Pelon, B. Bourachot, M. Cardon, P. Sirven, I. Magagna, L. Fuhrmann, C. Bernard, C. Bonneau, M. Kondratova, I. Kuperstein, A. Zinovyev, A.M. Givel, M.C. Parrini, V. Soumelis, A. Vincent-Salomon, F. Mechta-Grigoriou, Fibroblast Heterogeneity and Immunosuppressive Environment in Human Breast Cancer, Cancer Cell 33 (2018) 463–479 (e410).
[61] D. Ohlund, A. Handly-Santana, G. Biffi, E. Elyada, A.S. Almeida, M. Ponz-Sarvise, V. Corbo, T.E. Oni, S.A. Hearn, E.J. Lee, I.I. Chio, C.I. Hwang, H. Tiriac, L.A. Baker, D.D. Engle, C. Feig, A. Kultti, M. Egeblad, D.T. Fearon, J.M. Crawford, H. Clevers, Y. Park, D.A. Tuveson, Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer, J. Exp. Med. 214 (2017) 579–596.
[62] V.G. Cooke, V.S. LeBleu, D. Keskin, Z. Khan, J.T. O'Connell, Y. Teng, M.B. Duncan, L. Xie, G. Maeda, S. Vong, H. Sugimoto, R.M. Rocha, A. Damascena, R.R. Brentani, R. Kalluri, Pericyte depletion results in hypoxia-associated epithelial-to-mesenchymal transition and metastasis mediated by met signaling pathway, Cancer Cell 21 (2012) 66–81.
[63] J. Gore, M. Korc, Pancreatic cancer stroma: friend or foe? Cancer Cell 25 (2014) 711–712.
[64] F. Puleo, R. Nicolle, Y. Blum, J. Cros, L. Marisa, P. Demetter, E. Quertinmont, M. Svrcek, N. Elarouci, J. Iovanna, D. Franchimont, L. Verset, M.G. Galdon, J. Deviere, A. de Reynies, P. Laurent-Puig, J.L. Van Laethem, J.B. Bachet, R. Marechal, Stratification of Pancreatic Ductal Adenocarcinomas based on Tumor and Microenvironment Features, Gastroenterology 155 (2018) 1999–2013 (e1993).
[65] P. Bailey, D.K. Chang, K. Nones, A.L. Johns, A.M. Patch, M.C. Gingras, D.K. Miller, A.N. Christ, T.J. Bruxner, M.C. Quinn, C. Nourse, L.C. Murtaugh, I. Harliwong, S. Idrisoglu, S. Manning, E. Nourbakhsh, S. Wani, L. Fink, O. Holmes, V. Chin, M.J. Anderson, S. Kazakoff, C. Leonard, F. Newell, N. Waddell, S. Wood, Q. Xu, P.J. Wilson, N. Cloonan, K.S. Kassahn, D. Taylor, K. Quek, A. Robertson, L. Pantano, L. Mincarelli, L.N. Sanchez, L. Evers, J. Wu, M. Pinese, M.J. Cowley, M.D. Jones, E.K. Colvin, A.M. Nagrial, E.S. Humphrey, L.A. Chantrill, A. Mawson, J. Humphris, A. Chou, M. Pajic, C.J. Scarlett, A.V. Pinho, M. Giry-Laterriere, I. Rooman,

J.S. Samra, J.G. Kench, J.A. Lovell, N.D. Merrett, C.W. Toon, K. Epari, N.Q. Nguyen, A. Barbour, N. Zeps, K. Moran-Jones, N.B. Jamieson, J.S. Graham, F. Duthie, K. Oien, J. Hair, R. Grutzmann, A. Maitra, C.A. Iacobuzio-Donahue, C.L. Wolfgang, R.A. Morgan, R.T. Lawlor, V. Corbo, C. Bassi, B. Rusev, P. Capelli, R. Salvia, G. Tortora, D. Mukhopadhyay, G.M. Petersen, I. Australian Pancreatic Cancer Genome, D.M. Munzy, W.E. Fisher, S.A. Karim, J.R. Eshleman, R.H. Hruban, C. Pilarsky, J.P. Morton, O.J. Sansom, A. Scarpa, E.A. Musgrove, U.M. Bailey, O. Hofmann, R.L. Sutherland, D.A. Wheeler, A.J. Gill, R.A. Gibbs, J.V. Pearson, N. Waddell, A.V. Biankin, S.M. Grimmond, Genomic analyses identify molecular subtypes of pancreatic cancer, Nature 531 (2016) 47–52.

[66] N. Waddell, M. Pajic, A.M. Patch, D.K. Chang, K.S. Kassahn, P. Bailey, A.L. Johns, D. Miller, K. Nones, K. Quek, M.C. Quinn, A.J. Robertson, M.Z. Fadlullah, T.J. Bruxner, A.N. Christ, I. Harliwong, S. Idrisoglu, S. Manning, C. Nourse, E. Nourbakhsh, S. Wani, P.J. Wilson, E. Markham, N. Cloonan, M.J. Anderson, J.L. Fink, O. Holmes, S.H. Kazakoff, C. Leonard, F. Newell, B. Poudel, S. Song, D. Taylor, N. Waddell, S. Wood, Q. Xu, J. Wu, M. Pinese, M.J. Cowley, H.C. Lee, M.D. Jones, A.M. Nagrial, J. Humphris, L.A. Chantrill, V. Chin, A.M. Steinmann, A. Mawson, E.S. Humphrey, E.K. Colvin, A. Chou, C.J. Scarlett, A.V. Pinho, M. Giry-Laterriere, I. Rooman, J.S. Samra, J.G. Kench, J.A. Pettitt, N.D. Merrett, C. Toon, K. Epari, N.Q. Nguyen, A. Barbour, N. Zeps, N.B. Jamieson, J.S. Graham, S.P. Niclou, R. Bjerkvig, R. Grutzmann, D. Aust, R.H. Hruban, A. Maitra, C.A. Iacobuzio-Donahue, C.L. Wolfgang, R.A. Morgan, R.T. Lawlor, V. Corbo, C. Bassi, M. Falconi, G. Zamboni, G. Tortora, M.A. Tempero, I. Australian Pancreatic Cancer Genome, A.J. Gill, J.R. Eshleman, C. Pilarsky, A. Scarpa, E.A. Musgrove, J.V. Pearson, A.V. Biankin, S.M. Grimmond, Whole genomes redefine the mutational landscape of pancreatic cancer, Nature 518 (2015) 495–501.

[67] W.Q. Wang, L. Liu, H.C. Sun, Y.L. Fu, H.X. Xu, Z.T. Chai, Q.B. Zhang, L.Q. Kong, X.D. Zhu, L. Lu, Z.G. Ren, Z.Y. Tang, Tanshinone IIA inhibits metastasis after palliative resection of hepatocellular carcinoma and prolongs survival in part via vascular normalization, J. Hematol. Oncol. 5 (2012) 69.

[68] H. Griesmann, C. Drexel, N. Milosevic, B. Sipos, J. Rosendahl, T.M. Gress, P. Michl, Pharmacological macrophage inhibition decreases metastasis formation in a genetic model of pancreatic cancer, Gut 66 (2017) 1278–1285.

[69] V. Kunzmann, R.K. Ramanathan, D. Goldstein, H. Liu, S. Ferrara, B. Lu, M.F. Renschler, D.D. Von Hoff, Tumor reduction in primary and metastatic pancreatic cancer lesions with nab-paclitaxel and gemcitabine: an exploratory analysis from a phase 3 study, Pancreas 46 (2017) 203–208.

[70] T.A. Mace, R. Shakya, J.R. Pitarresi, B. Swanson, C.W. McQuinn, S. Loftus, E. Nordquist, Z. Cruz-Monserrate, L. Yu, G. Young, X. Zhong, T.A. Zimmers, M.C. Ostrowski, T. Ludwig, M. Bloomston, T. Bekaii-Saab, G.B. Lesinski, IL-6 and PD-L1 antibody blockade combination therapy reduces tumour progression in murine models of pancreatic cancer, Gut 67 (2018) 320–332.