ISSN: 2755-0117

Journal of Oncology Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Pancreatic Cancer Therapeutics are we doing things Right?

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ABSTRACT

Pancreatic adenocarcinoma (PDAC) is one of the most lethal cancers. Among su-pramesocolic cancers, PDAC carries the worst prognosis because early detection re-mains a difficult task. Many treatment regimens failed to show improvement in terms of OS and DFS. In this review, we try to focus on PDAC from a molecular perspective. We identified how the 10 hallmarks of cancer apply in PDAC. K-ras mutation (the setter) was the triggering factor for all of them. Moreover, G12D mutation is a crucial step for PDAC to occur. Since this gene has many downstream pathways (spikers), it's hard to hope for an effective treatment for each downstream mutation. Therefore, further re-search is required to find therapeutic drugs to target this mutation, the K-ras G12D.

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Received: October 31, 2025; **Accepted:** November 04, 2025; **Published:** November 13, 2025

Introduction

Pancreatic adenocarcinoma (PDAC) is one of the most lethal cancers. Less than 5% of patients diagnosed with PAC will remain alive at the end of a 5-year follow-up period [1]. It is the 3rd leading cause of cancer-related deaths in the United States.

Many regimens have been proposed: some had impact on downstaging; others on Pro-gression Free-Survival (PFS), but little benefits were observed in terms of Overall Sur-vival (OS) and cure rates [2]. Among the supramesocolic cancers, PAC carries the worst prognosis because early detection remains a difficult task [3]. A recent meta-analysis showed that chemotherapy could increase survival in 30% of cases, however adding radiotherapy to the adjuvant regimen, without adding any benefit, resulted in increased toxicity [4]. A look in depth into the early RCTs that were done to compare between dif-ferent regimens, one could notice little benefit of one protocol over the other. In the ES-PAC-3 trial, [5]. Gemcitabine resulted in OS of 23.6 months when compared to 5-FU/LV (23 months). When it comes to advanced pancreatic cancer, OS varied between 5 and 11 months [6]. Multiple drug combination regimens such as FOLFORINOX, were able to attain a 11.1-month median survival [4].

With the advances in immunotherapy, new drugs were tried in patients with pancreatic cancer. To mention, few trials were being recruited and only 2 were achieved and ended up with disappointing results [3-5].

In this review, we will be trying to understand the aggressiveness of PAC, by dissecting it's pathobiology while reviewing the anatomy, histology, pathology and molecular biol-ogy, in order to find out, what are the "Hanahan" Hallmarks that apply to PAC.

Anatomy and Histology

The pancreas is a retroperitoneal organ. It has a close relation with its surrounding or-gans, such as the duodenum, the biliary tree and the mesenteric vessels (figure 1).

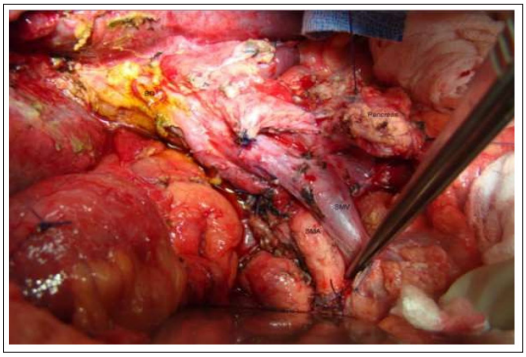


Figure 1: Shows the Close Relationship between the Pancreas and its Surroundings (SMA: Superior Mesenteric Artery; SMV: Superior Mesenteric vein, BD: Bile Duct)

Histologically, the pancreas is formed by exocrine and endocrine group of cells. Almost 90% of the gland is formed by exocrine cells, which explains why pancreatic ductal carcinoma comprises about 80% of pancreatic cancers, and thus it will be the subject of our review. The other type of pancreatic cancer arising from the endocrine cells is the NETs. Some of the NETs occur in the head of the pancreas in association with Von-Recklighausen disease.

Pancreatic cells are enveloped by a thin layer of connective tissue. This afibrotic capsule extends between the acini, dividing them into lobules, causing a lobular aspect of the pancreatic gland [7].

Different cellular populations could be retrieved from human pan-creas, including stellate cells, exocrine cells, ductal cells and endocrine cells [7-9].

Stellate cells, designated as PSCs (Pancreatic stellate cells), are thought to play an im-portant role in the inflammatory desmoplastic reaction in pancreatic cancer. The fibrotic response is sometimes seen in the naked eye (figure 2), the clamp is pointing at the desmoplastic reaction secondary to pancreatic cancer, that can be seen in naked eyes in this case (57 year old male with PDAC) and is thought to be responsible of the great re-sistance of pancreatic cancer to different treatment regimens.

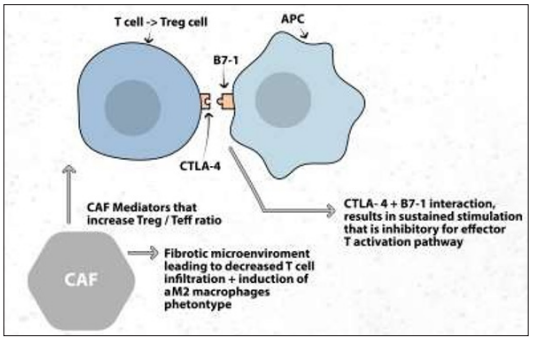


Figure 2

Stellate cells have a fibroblastic shape. They are seen on electron microscopy and are very close to the acinar cells [9,10]. Normally stellate cells are responsible for the syn-thesis of fibrotic layer, in response to injury, oxidative stress and ethanol exposure [10].

PDAC (Pancreatic ductal carcinoma), arise in acinar cells that undergo ductal metaplasia. Three preneoplastic lesions can lead to this cancer: IPMN (Intraductal Papillary Mucin-ous Neoplasm), MCN (Mucinous Cystic Neoplasm) and PanIN (Pancreatic Intraepitheli-al Neoplasia). They are graded differently from cancer of the viscera.

The pancreas is divided into 4 parts: the head, body, tail and the uncinate process. It lies anterior to the superior mesenteric vessels except for the uncinate process, and is in close relationship to the duodenum, stomach and bile ducts.

PDAC And Pre-Neoplastic Gene Signatures

As we mentioned previously, there are 3 precursor types for PDACs. For decades, it was thought that ductal cells undergo dysplastic changes leading to cancer of the pancreas; however, refined animal studies postulated that acinar to ductal metaplasia is the earliest precursor lesion leading to carcinoma [11]. ADM (acinar to ductal mucosa) are observed in patients with a history of chronic pancreatitis. Also, epithelial to mesenchymal meta-plasia is seen in pancreatic cancer (known as fibrosis) that accompanies tumorigenesis [12].

Regarding cellular population in pancreatic cancer, immune-mediators such as interleu-kins and tumor growth factors, are responsible for the recruitment of new type of cells: T helper cells, T reg cells and Macrophages [2].

In case of pancreatitis, this metaplasia usually resolves once the stressful agent has been removed. However, not all patients with chronic pancreatitis would develop cancer, nor all patients with pancreatic cancer have had a history of pancreatitis [13].

In one preclinical study conducted on mice, only mice with Kras mutation G12D showed progression from ADM to PAN-in, when pancreatitis has been induced [14].

Wild type (k-ras) mice showed regeneration of normal pancreatic architecture, in a self resolving phenomena, comprising 3 phases: acute pancreatitis, regeneration and refine-ment [14]. Those steps were absent in mice harboring the G12D mutation of the K-ras oncogene.

Further studies have shown that inflammatory mediators, such as TGF-b plays a major role in initiation of pancreatic tumoregenesis [11].

So, inflammation by itself is a triggering effect, that needs a predisposing mutation, for the carcinogenesis or dysplastic cascade to occur. It is believed that a sustained K-ras mutation could lead to carcinogenesis of the pancreatic parenchyma [1].

The dysplastic cascade in pancreatic cancer could be summarized by the following: ADM → PAN-in 1 → PAN-in 2 → PAN-in 3 → Cancer.

To define the genetic signature of each different stage, a retrospective archival study, reviewed 21 laser partial pancreatectomies performed for chronic pancreatitis [13].

Early genetic events seen in PanIN-1 and PanIN-2 are K-ras mutations, p16 loss and te-lomerase shortening other late genetic mutations affect P53, SMAD4 loss and BRCA2 mutations [1,15]. These later mutations are usually seen in PanIN-3. Actually, about 90 % of PDAC harbour K-ras mutations); however sustained K-ras signalling is required for PDAC to occur [15,16].

PDAC process is accelerated when further mutations are being added to the driven on-cogenic mutation of K-ras [17].

K-ras is a transmembranous cellular protein that belongs to the G superfamily and it's activated once it binds to GTP and deactivated when it combines with GDP [6]. Activa-tion of K-ras leads to activation of downstream effectors such as PI3 kinase pathway and the **RAF→MEK→ERK pathway [17]**. Preclinical studies have shown the RAF→MEK→ERK is implicated in pancreatic carcinogenesis [18]. Other studies have shown that P53 and P16 mutations are found in patients with chronic pancreatitis (CP), and necessary for the PDAC to occur [13].

To Summarize:

K-ras mutation + CP → PDAC

or

G12D K-ras mutation + P53 /P16 mutation → PDAC

Now we can understand better why obesity, alcohol, and other conditions causing CP of the pancreas predispose to PDAC.

The K-ras activation is not a single biochemical reaction since it has upstream regulatory effectors and downstream ones.

The conclusion is that when a mutation of the K-ras gene occurs, sustained activation of this gene predisposes to PDAC, but sustained activation could be the result of upstream effectors' alterations or lower level (downstream) effectors mutations. Furthermore, oth-er mutations affecting tumour suppressor genes (TSP) have to appear with a sustained K-ras→ RAF → MEK→ ERK pathway activation, for the cancer to occur [1].

In conclusion, a sustained K-ras→ RAF → MEK→ ERK pathway activation could be the result of upstream deregulation, downstream mutations or a gene mutation.

A particular feature leading to PDAC and rendering it resistant to different chemothera-py regimens is the desmoplastic nature of this cancer which leads to T cells chemotaxis and alterations of some local immune effectors [12].

In the following sections we will try to dissect the pathogenesis of PDAC, from a Han-nahan perspective, in order to find answers and new questions about PDAC. Each hall-mark will be studied separately, starting arbitrarily by the "evading growth suppressors" and proceeding "clockwise".

Evading Growth Suppressors and PDAC

Cyclins and cyclin dependent kinases are enzymes that regulate the cell cycle, allowing its transition from G0/G1 to S phase where all necessary proteins for transcription are synthesized. D- cyclins activate CDK4/6, which phosphorylate the retinoblastoma tu-mour suppressor protein (Rb) leading to its inactivation.

In many PDAC, D-cyclins' expression is altered in cell cycle transition [6-21].

In one study conducted on PDAC human cell lines, cyclin D3 suppression resulted in a more pronounced decreased PDAC cell proliferation, while compared to CKDN-1 sup-pression [6]. In one prospective clinical study, the polymorphism of Cyclin D1 gene (CCND1) was analyzed as a prognostic survival for patients with PDAC following Whipple procedure [19]. The target was G870A polymorphism, where patients with GG polymorphism, showed better survival rates than patients with either AG polymorphism or AA poly-morphism.

To summarize the results of this study, patients with Cyclin D1 G870A polymorphism A/A have had a median survival of 15.1 months, versus 21.5 months for A/G, and 29.4 months for G/G with a P value < 0.03. Another study, proved that the Transcription fac-tor "Six1" targets the CCND1, and thus six-1 participates in the tumourigenesis of PDAC.

In other terms, abnormally high levels of Six1 are found in patients with PDAC [20]. In a preclinical study, PANC-1 cells harbouring cyclin D1 antisense cDNA in a tetracy-cline-inducible vector, were xenografted into mice. Mice were then assigned to group 1 (drink water that contain tetracycline) vs group 2 (drink water without tetracycline) [21]. Mice without tetracycline inducible signals, have had evidence of tumour growth retar-dation with areas of necrosis within the tumour. This study enlightens the important role of CDKN1 signalling in PDAC. It's noteworthy mentioning, that PANC1 are carcinoma cell line from human pancreas.

Clinical Applications

Cyclins play a major role in a cell lifecycle, and any sustained activation of CDKN1 or CKDN3 is thought to have an effector role in PDAC. Some studies could be of clinical use, such as the GG polymorphism and dosage of six-1 transcription factor [19,20].

Avoiding Immune Destruction and PDAC (Avoiding $CD8^+$)

This hallmark was studied in depth for PDAC since aggressive PDAC associated cells express immunosuppressive antigens, such as B7-1 also known as CD274, that results in poorer outcomes and decreased survival [22]. It is well known that innate and acquired immunity are important effectors in protecting against cancer initiation, invasion and metastasis [2,23,24].

PDAC cells trigger a suppressive immunity microenvironment (PDAC stroma). This mi-cro-environment shows increased number of myeloid derived cells [25]. Essential im-munosuppressive cells are macrophages (M2 phenotype), regulatory T- cells (T-regs) and CAF (cancer associated fibroblasts) [2].

It's noteworthy mentioning that PSC (pancreas stellate cells), fibroblasts and bone mar-row derived mesenchymal cells will undergo differentiation into CAFs [26]. CAFs then secrete pro-inflammatory mediators that result in increased Treg/Teff ratio where Treg are regulatory T cells and Teff are effector T cells [3,27]. By increasing Tregs popula-tion, these later cells will induce exclusion of "CD8+ Tcells" differentiation, via a cellu-lar membrane ligand: the CTLA-4 [1-3]. CTLA-4 or CD152, is an immune checkpoint, that is present on T cell surface. This checkpoint regulates early stages of T-cell activa-tion by binding to specific antigens on APC (Antigen Presenting Cells) [1,26]. The anti-gen that binds to CTLA-4 is the B7-1 (attenuates T-cell signaling) and leads to dediffer-entiation into Teffs. The binding surface between B7-1 and CTLA-4 is so small and ex-hibits a high degree of geometrical conformity, owing to what we do call "Zipper oli-gomerization" [26]. This zipper-like bond, is thought to be the cause of a stable inhibito-ry signalling complex, that many clinical and preclinical studies have tried to target. CD4+ T cells that infiltrate tumour tissues express high levels of PD-1 (check point in-hibitor), that binds to PD-L1 on cancer cells, leading to an early apoptosis of those T cells [28].

Furthermore, CAF will inhibit proinflammatory interleukin secretions, and will promote macrophage differentiation into phenotype 2 (Known as M2) rather than M1 [29].

To recapitulate, CAF will recruit T reg cells (PD-1 +), inhibit the recruitment of CD8 (+) cells and promote M1 (tumour suppressive) to M2 (tumour promoter) macrophages tran-sition [29]. All these changes are in favour for cancer development and progression.

In addition, CAFs contribute into the genesis of the fibrotic environment in PDAC [28,29].

Figure 3 Summarizes the effects of CAF (cancer associated fibroblasts) role in evading immune response.

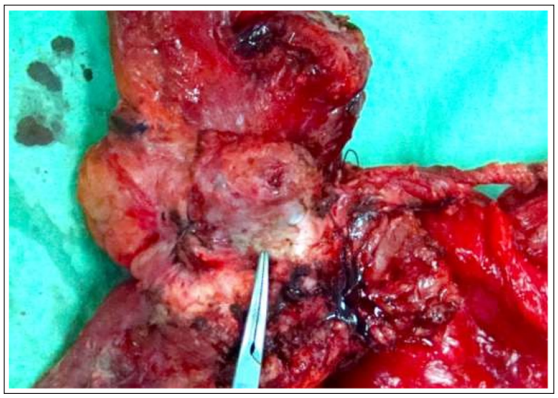


Figure 3: The Presence of Short Telomeres in Viable Cells, is the Result of a Telomer-ase Activity as we can See in this Picture

The fibrotic microenvironment also plays a major role in the immunity escaping process. The stiff stroma associated with PDAC induces a mechanical stimulation of the JAK-STAT3

pathway, resulting in release of growth factors, immune cells deregulation and increased cancer aggressiveness [30].
In summary, CAF induces immune deregulation by:

- Increasing Treg/Teff ratio (via a CTLA-4 induced mechanism)
- Favoring M2 phenotype macrophage differentiation
- Synthetizing a desmoplastic stroma
- Binding to PD-1 checkpoint on Treg cells, resulting in early apoptosis of these cells.

Clinical Application
CTLA-4 activation can attenuate cellular mediated immunity against cancer, and has been the subject of many preclinical and clinical trials [3,29]. Iplimumab (monoclonal antibody against CTLA-4) has been evaluated as a potential treatment for patients with PDAC [31]. In this trial, 27 patients with advanced PDAC received iplimumab at a dose of 3mg/kg for a maximum of 48 doses [31]. In this study results were disappointing, and tumour regression were not detected on paraclinical investigations. Another clinical trial, the NCT00836407 which is a prospective randomized study that divided 30 patients into 2 arms: arm 1 patients received Iplimumab alone vs arm 2 where patients received Ipli-mumab + PDAC vaccine [32]. Some features of tumour regression were observed, such as decrease in CA19-9 and a relatively stable disease in about 3 patients. Many other studies are recruiting, and new drugs are being tested, such anti PD-1 and anti PD-L1 [1,2].

Despite promising results in melanoma, CTLA-4 targeted therapy has failed to demon-strate efficacy in PDAC [2,3,29]. Regarding melanoma, targeted therapy improved CD8+ T cell activity, infiltration and ratio within tumours. However, this was not true for PDAC. Preclinical studies conducted on mice have demonstrated that adding targeted therapy to kras mutated mice did not improve CD8 + T cell infiltration into tumour tis-sues [30-33]. So, what target are we missing in PDAC?

The answer appears to be simple: Target the peritumoural stroma! Many preclinical experiments that were conducted on mice showed improved cytotoxic activity when CAF were blocked or when CXCL12 (CAF secreted interleukin) was tar-geted [11,34]. But further studies have shown that this stroma is so heterogenous in terms of cell population and varied widely in biochemical composition [35].

This pancreatic microenvironment is so complex and contains different types of mul-tipotent (bone marrow derived mesenchymal cells) cells that are in continuous interac-tion with their neighbour cancer cells [34]. This could explain the complexity and the difficulty in targeting checkpoint inhibitors in PDAC. Furthermore, there are 2 types of TAM (tumour associated macrophages) in PDAC: monocytes deriving and embryonic derived [36]. The later macrophages have no role in antigen presentation, rather their major function is to secrete a fibrotic resistant extracellular matrix.

Enabling Replicative Immortality
It is well known that with each cellular division telomeres become shorter [37]. When the telomeric DNA material becomes uncapped, cellular senescence will be induced via a P53/P16 pathway [37,38]. However, when P16 and P53 are mutated (seen in PDAC), cellular division continues to take place, acquiring immortality as well as DNA muta-tions. Even in the setting of P16/P53 mutations, when telomeres become too short, the cell will suffer what we call the telomere crisis inducing cell death (figure 4) [38].

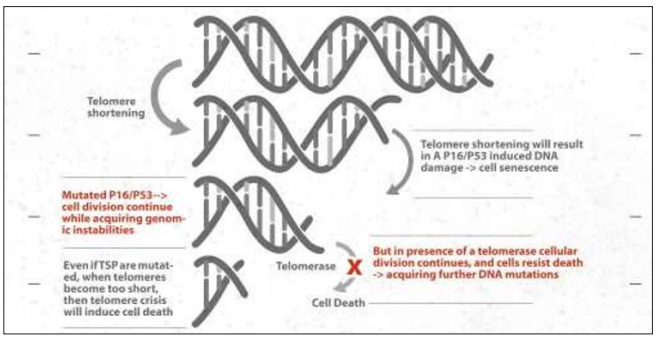


Figure 4: The Set and Spike Maneuver; we Assimilated our Immune System to a Vol-leyball net, and the k-ras to a Setter Player. The spikers Could be any Other Mutation or Hallmark Including Inflammation, Cox-2 over Expression, P16/TP53 Mutation or CCI-2/CCR up-regulation

The presence of a telomerase could lead to a cell death escape by adding DNA material to the short telomeres [37]. This explains why short telomeres are one of the earliest signs of PDAC and are usually seen in PAN-in1 [37-39].

To recapitulate, short telomeres seen in in Pan-in1 and early PDAC are suggestive of the presence of telomerase activity. Targeting these telomerase can decrease PDAC lifespan [38-40].

In a preclinical study, targeting PDAC cell lines with Imetelstat (GRN163L), a telomer-ase inhibitor has shown to decrease PDAC life span (37). Chronic exposure to GRN163L has led to telomeres shortening and cell crisis induction with subsequent loss of cellular cultures in different cell lines of PDAC [40].

Clinical Application
In a case control study performed by skinner et al, short telomeres were associated with an increased risk of PDAC [38]. In this study, telomere length was measured in periph-eral blood leukocytes using PCR techniques. 499 cases of PDAC were compared to con-trols (about 963 cancer free patients). This was suggestive of an inverse linear correla-tion between telomere length and the risk of having PDAC.

Tumor Promoting Inflammation
Tumours are like any wound or any inflammatory reaction. However, these "wounds don't heal".
In one clinical study, tissues from 20 patients with PDAC were studied and peripheral blood was drawn to evaluate the peripheral inflammatory response in those patients [41].

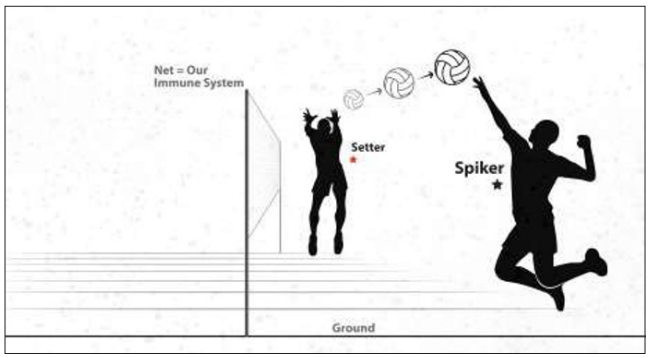
- Regarding the local tumour infiltration: cells expressing CD33+ and CD136+ were detected in tumour tissues, whereas CD4+ PD-1 + were detected in regional lymph nodes. Those Lymph nodes showed low levels of CD8+ T cells (explained in details in section 2).
- Also, high levels of Il-6, Il-7 and Il-15 were detected in tumour tissues.
- Regarding peripheral blood: high levels of different immune cells were detected, no-tably monocytes and PD-1 CD4+ cells.

CD 136+ is suggestive of macrophage M2 phenotype which is a tumour promoter. High levels of CD4+ PD-1+ cells mean that Treg/Teff is increased. Interleukins promote desmoplastic reaction in the peritumoural "neighbourhood". Although this issue was discussed in section 2, what's unique in this study is the systemic inflammatory re-sponse that was similar to the regional reaction. High levels of peripheral CD4+ PD-1+ cells were found, which is

thought to contribute to systemic chemotherapy resistance [1,41]. The hallmark of the inflammatory reaction in PDAC comes from the infiltration of monocytes and their differentiation into M2 promoting phenotypes.

Another clinical study focused on peripheral inflammatory monocytes in patients with PDAC [42]. According to this case control study, patients who showed high levels of monocytes in their peripheral blood have had the worst prognosis. Using murine models, CCL2 (chemokine) secreted by PAN-in1, was found to recruit monocytes and to induce their differentiation into M2 macrophages [42].

Many preclinical studies have focused on studying inflammatory mediators' role in PDAC (42-44). COX-2 is thought to promote PDAC progression via modulating a fibro-blast growth factor (FGF-2) [43]. In this study, celecoxib rendered PAN-in1 cells cul-tures resistant to FGf-2 [43]. Mice models were also used to evaluate the role of COX-2 in PDAC initiation [44]. Although overexpression of COX-2 promotes tumour progres-sion, COX-2 overexpression alone without K-ras mutation resulted only in acinar to ductal mucosa with no evidence of PDAC development [44]. This was also highlighted in the introduction, where chronic pancreatitis resulted in TSP mutations but in the ab-sence of a K-ras mutation, progression into a PDAC was not evident. K-ras G12D and inflammation are both needed for PDAC to occur and we would like to call this phe-nomena, a "volleyball like" cancer set and spike (figure 5) where k-ras is a triggering mutation or the player who passes the ball for his colleague (the inflammation) to spike it aggressively overcoming the "net ", is our immune system. In this "set and spike" ma-neuver, we have only one setter, the k-ras mutation, whereas many effectors could play the role of the spiker (the hitter): pancreatitis, overexpression of Cox-2, P16/p53 muta-tions, FGF-2, EGF-2, angiogenesis and up-regulation of chemokines and their receptors (CCl2/CCR2).



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Clinical Applications

Many preclinical studies have shown some efficacy of COX-2 inhibitors in preventing PDAC progression [44,45]. One of studies combined atorvastatin to celecoxib and tipi-farnib showed strong inhibition of PDAC growth in xenografted mice [45].

A phase II clinical trial conducted on 83 patients with advanced PDAC failed to show any advantage for adding COX-2 inhibitor to the treatment regimen [46].

Interestingly, in one case report of unresectable pancreatic head desmoid tumour, COX-2 inhibitor resulted in complete remission for a period of 24 months [47].

Invasion, Progression and Metastasis

Pan-In1 or PDAC precursor cells present some degree of architectural atypia, by ex-pressing the surface cell apomurine (MUC-1) [1]. It's noteworthy mentioning that PDAC originate from the acinar cells that have undergone ductal metaplasia and that EMT (epi-thelial to mesenchymal transition) occur in the early stages of the disease [12]. They could be seen with Pan-In2 and Pan-In3 [1,12]. However, pancreatic cancer cells do not undergo only EMT but also they do experience MET (mesenchymal to epithelial transi-tion) that is induced by perineural Schwann cells, that's why perineural invasion is a common feature in DPAC [48].

Cell lines and mice model studies have postulated that IL-6 secreted by PSCs promotes EMT [49]. EMT is the one of the crucial steps for invasion (and later on metastasis) to occur. EMT means that the cancer cell is able to go through the basement membrane of the tissue thus to travel far away via the blood stream [1,12,48]. Other inflammatory cells, such as M2 Macrophages, promote cellular invasion and EMT process [50]. Also, PSCs activated by SHH (Sonic Hedgehog) protein promotes invasion, EMT and metasta-sis [51]. Bone marrow derived myeloid cells that express CD133 can also induce EMT and invasion by activating NF-Kb (Nuclear factor kappa light chain of activated B cells) pathway [52].

In controversy, PSCs seem to be the main effectors in this loop of interaction, and the best PSCs induced EMT pathway that was studied in depth was the HGF/C-met pathway [53,54].

The Hepatocyte Growth Factor (HGF) is secreted by PSCs to activate epithelial cancer cells receptors (c-met) in order to promote EMT, invasion and metastasis. HGF when binds to C-met increases DNA synthesis, proliferation and EMT [53].

Clinical Applications

Some paraclinical experiments have shown promising results by blocking HGF/C-met pathway [53,54]. In one preclinical study, association of gemcitabine with a HGF/c-met antagonist, resulted in decreased number of distant metastases in xenografted mice [53].

Inducing Tumor Angiogenesis

PDAC tissues are poorly vascularized due to the excessive fibrotic stroma secreted by PSC's [54]. Paradoxically, this hypoxia will switch on angiogenesis mechanism via dif-ferent pathways. One of the proposed pathways is mediated via periostin (POSTN) that activates ERK/VEGF pathway leading to over expression of VEGF (vasculature Endo-thelial Growth Factor) [56]. Angiogenic switch could also be induced by Metalloprotein-ase -9 (MMP-9) [57].

A case control study compared PDAC patients VEGF mRNA serum to healthy controls and found that PDAC patients had high levels of VEGF mRNA with the point mutation +450G/C [58].

Targeting VEGF, MMp-9 or Periostin resulted in decreased tumour invasion and less me-tastasis in preclinical studies [1,34,57].

Clinical Applications

Many clinical trials are conducted for patients with advanced PDAC. About 11 trials are recruiting or in process to assess the role of anti-VEGF in PDAC therapy [57-59]. To date, one trial "NCT00185588", showed promising results. In this phase I/II clinical study, about 33 patients showed evidence of PFS in a time frame of 12 months when vatalanib an anti-VEGF agent was

added to the conventional regimen (gemcitabine).

Genomic Instability and PARP Inhibitors

Due to the sustained replication of genomic materials and in the presence of short telo-meres (as described in section 3), genomic mutations occur leading to DNA material in-stability.

Normally, cells acquiring this arsenal of DNA mutations follow the death pathway. PARP–Poly (ADP-ribose) Polymerase play a major role with BRCA-1 and BRCA-2 pro-teins in DNA damage repair [60]. BRCA-1 and BRCA-2 are proteins that stabilize tran-scriptional hemodynamics by binding to Rad 51. BRCA-1 and BRCA-2 usually promote homologous recombination (DNA repair mechanism). When those 2 proteins are mutat-ed, then PARP inhibition results in tumor cell death [60,61].

Women carrying BRCA mutations (whether BRAC1 or BRCA-2) are at increased risk for developing pancreatic cancers. In one prospective study about 5149 patients with BRCA mutations were followed for a mean of 1.95 years [62]. About 8 cases of pan-creatic cancers developed during follow-up period and the 5-year overall survival fol-lowing PDAC were respectively: 4% for BRCA-1 patients and 5% for BRCA-2 muta-tions.

Clinical Applications

Since BRCA mutation is favorable for PARP inhibition, clinical trials are being conduct-ed in order to study the efficacy of PARP inhibition when combined to other chemo-therapy regimens [(NCT01585805) and (NCT02184195)] in BRCA+ pancreatic cancers. One clinical study conducted on 16 patients with BRCA + PDAC failed to show a con-siderable improvement after patients were exposed to Veliparib, a PARP inhibitor drug [63].

Apoptosis a Double Edged Sword

When it comes to apoptosis, PDAC cells use this tool as a double edged sword. Firstly, PDAC cells can overexpress BCL-2 /FlICE proteins that have anti-apoptotic activity or PDAC can use PD-L1 to induce T- cellular apoptosis and escape immune surveillance, as described in section 2 [64,65]. Actually we have 2 types of apoptotic proteins, the BH3 family that induces apoptosis and the BCL-2 like proteins that inhibits apoptosis [64]. Using cellular cultures, it has been demonstrated that Gemcitabine induces cellular death by promoting apoptosis [65,66]. Cell line cultures demonstrated high surface lev-els of FLICE proteins that have anti-apoptotic function [65]. The concentrations of FLICE (c-Flip) were decreased after cell lines were exposed to Gemcitabine. In sum-mary, PDAC cells express high levels of anti-apoptotic proteins such as FLICE or BCL-2 in order to escape apoptosis.

In one preclinical study on subcutaneous xenografts, adding Sabutoclax (a BH3 apoptot-ic mimetic) to minocycline resulted in a potent inhibition of pancreatic tumor cell growth [67]. Since Gemcitabine is the drug of choice for PDAC, and since it induces apoptosis, it seems that future development of a safe clinical BH3 mimetic will have a synergistic therapeutic effect, perhaps longer OS curves will be then drawn [66,67].

Clinical Applications

Using Mesh terms (pancreas and (Bcl-2 or Bh3 or apoptosis)) revealed no evidence of ongoing clinical trials on humans when searching into PubMed. However, there is a clin-ical phase 1 trial that has been performed in which CPI-613 (a molecule that induces apoptosis by targeting directly the mitochondria) in combination with modified FOLFI-RINOX (oxaliplatin at 65 mg/m2, leucovorin at 400 mg/m2, irinotecan at 140 mg/m2, and fluorouracil 400 mg/m2 bolus followed by 2400 mg/m2 over 46 h) were given for 20 patients with PDAC [68]. Complete or partial response were observed in 61% of the participants.

Regarding PD-1/PD-L1 targeted therapy, the other edge of the sword, many clinical trials are ongoing such as: NCT02331251, NCT02305186, and NCT01714739.

Metabolism Shift and Glycolysis Inhibitors

Desmoplastic reaction that accompanies PDAC induces hypoxia and tissue suffering. To adapt, cancer cells shift their metabolism from oxidative phosphorylation towards aero-bic glycolysis with a preferential lactate shift. This is known as the Warburg effect [69,70]. Lactate production promotes tumour growth and proliferation. Elevated glyco-lytic metabolism is seen in patients with PDAC and this is mainly the result of a K-ras or a Tumour Suppressor gene mutation (TSP) [71].

Clinical Applications

Many proteins such as transcriptional factors influence metabolic changes that accom-pany PDAC [72,73]. High levels of TCF7L2 (Transcription Factor &-Like2/Transcription factor 4) correlated significantly with poorer outcomes in patients with PDAC [71]. This transcriptional factor promotes aerobic glycolysis in cancer cells and that explains why patients with high levels of TCF7L2 levels had decreased OS rates when compared to patients with lower levels (6.6 months vs 36 months P<0.001). The F-box WD repeat domain containing -7 (FBW7), suppresses glycolysis via the KRAS dependent/Ras–Raf–MEK–ERK pathway [72]. Patients with mutated K-ras will have the effect of FBW7 inhibited, thus promoting glycolysis and tumour promotion.

One preclinical trial showed that restricting glucose intake causes improvement in tu-mour response to chemo-radiation therapy [74]. A retrospective study conducted by Iar-robino et al trial showed that statins also increased tumor response to chemoradiation in patients with PDAC [75]. However, preclinical studies have shown that by targeting the glycolysis only, cancer cells will shift their metabolism towards oxidative phosphoryla-tion thats why, mitochondrial redox complexes are now also subjected to targeted thera-py [71,76].

EGFR Receptors and PDAC

As mentioned before in previous sections, the K-ras is a small proto-oncogene protein that is highly dynamic and is associated with multiple downstream activation pathways such as: Ref/MEK/ERK , PI3K, PDk1, Ranf1 P120GAP and many others [77]. EGFR is the upstream regulator of K-ras and its activation results in the stimulation of a cosmo-politan population of intracellular effectors (figure 6).

Furthermore, many other Tyrosine Kinase receptors can interfere directly or indirectly with one or more of these activation pathways (figure 6).

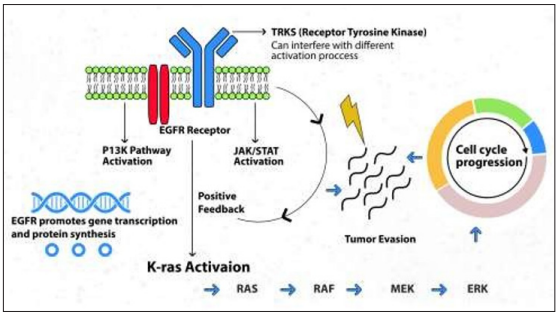

Figure 6: EGFR/K-ras Activation Results in the Stimulation of a Cosmopolitan Popula-tion of different Downstream Effectors

K-ras mutation alone is essential for PDAC to occur, and in some preclinical studies, it has been demonstrated that K-ras activation can result in acinar to ductal metaplasia [78]. In mice models, Acinar cells whether carrying a mutated K-ras genes or not, did not express any kind of EGFR receptor [79]. However, PanIN cells derived from these acinar cells showed high numbers of EGFR [79,80]. Other mutations described previ-ously, such as P16 or P53 could have a role in the transition of ADM to PANIn and maybe the expression of EGFR which could be the result of a paracrine activity [78-81]. It has been demonstrated that adding EGFR activation to cell cultures increases the number of metaplastic figures and promotes tumour proliferation and invasion [78].

In summary, EGFR are essential for tumour induction and progression thus patients with high levels of EGFR have had poorer prognosis and presented with more advanced dis-eases [81].

Clinical Applications

A recent meta-analysis of 28 studies, with a total of 3718 patients showed that adding EGFR-targeted treatment to chemotherapy did not improve progression-free or OS in patients with advanced PDAC [82]. Furthermore, EGFR targeted therapy was associated with increased treatment related death and toxicity. More recent RCT also failed to show any benefit for adding EGFR targeted therapy to chemotherapeutic regimens. In a phase II clinical trial, Erlotininb, an EGFR inhibitor, failed to show any utility for patients with PDAC [83]. Adding Vandetanib (EGFR inhibitor) to Gemcitabine did not improve OS when compared to Gemcitabine alone in the vip trial [84]. EGFR targeting seems to be complicated, since the downstream effectors could be mutated or activated, regardless of the EGFR gene status.

Conclusion

As we can see from this brief review, the 10 hallmarks of cancer apply to PDAC.

So, let's answer our question: Are we doing things the right way? To date none of the clinical trials targeting whether PD-1, PDL-1 or CTLA-4 has shown any superiority over Gemcitabine. This is due to the fact that K-ras mutation stimulates many downstream and parallel effectors, and thus it's hard to control. As we have mentioned previously in this paper, K-ras is the setter, and all the 10 hallmarks of Hanahan that apply in PDAC, are the hitter. So, why not try targeting directly the setter? Some clinical studies, are try-ing to target K-ras directly by using exosomes [85,86]. Until these results gain success, we do believe that PDAC will remain a cancer that is hard to control and treat.

Additional Information

Ethical approval and consent to participate does not apply to this review article nor does consent to publish. There is no conflict of interest that I should disclose.

There is no financial support either. There is no relevant professional or financial inter-ests. All of the above mentioned authors contributed to this review.

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