World Journal of Gastrointestinal Oncology

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DOI: 10.4251/wjgo.v8.i4.380

World J Gastrointest Oncol 2016 April 15; 8(4): 380-388
ISSN 1948-5204 (online)
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REVIEW

Targeting inflammation in pancreatic cancer: Clinical translation

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Author contributions: Steele CW drafted this review; Kaur Gill NA contributed the literature review and table; Jamieson NB and Carter CR edited the final manuscript.

Conflict-of-interest statement: We have no conflicts of interest to disclose.

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Received: November 29, 2015
Peer-review started: November 30, 2015
First decision: December 28, 2015
Revised: January 5, 2016
Accepted: February 14, 2016
Article in press: February 16, 2016
Published online: April 15, 2016

Abstract

Preclinical modelling studies are beginning to aid development of therapies targeted against key regulators of pancreatic cancer progression. Pancreatic cancer is an aggressive, stromally-rich tumor, from which few people survive. Within the tumor microenvironment cellular and extracellular components exist, shielding tumor cells from immune cell clearance, and chemotherapy, enhancing progression of the disease. The cellular component of this microenvironment consists mainly of stellate cells and inflammatory cells. New findings suggest that manipulation of the cellular component of the tumor microenvironment is possible to promote immune cell killing of tumor cells. Here we explore possible immunogenic therapeutic strategies. Additionally extracellular stromal elements play a key role in protecting tumor cells from chemotherapies targeted at the pancreas. We describe the experimental findings and the pitfalls associated with translation of stromally targeted therapies to clinical trial. Finally, we discuss the key inflammatory signal transducers activated subsequent to driver mutations in oncogenic Kras in pancreatic cancer. We present the preclinical findings that have led to successful early trials of STAT3 inhibitors in pancreatic adenocarcinoma.

Key words: Pancreatic cancer; Inflammation; Stroma; Microenvironment

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Core tip: Many advances have been made in preclinical assessment of therapies in pancreatic cancer. Here we review the successes and failures of translation to clinical trial of therapies targeting the pancreatic cancer microenvironment. Using data from preclinical trials we expose opportunities for further clinical trial within pancreatic cancer. We focus on therapies that modulate the immune response to pancreatic cancer, stromally active therapies and therapies targeting inflammatory signal transduction that are key in pancreatic cancer progression. We provide experimental results that have led to clinical trial and those findings that may be exploited in future. We attempt to rationalize the failure of certain therapies to

translate to clinical practice and provide a realistic overview of why at present tumor microenvironment targeted therapies are not licensed in pancreatic cancer.

Steele CW, Kaur Gill NA, Jamieson NB, Carter CR. Targeting inflammation in pancreatic cancer: Clinical translation. *World J Gastrointest Oncol* 2016; 8(4): 380-388 Available from: URL: http://www.wjgnet.com/1948-5204/full/v8/i4/380.htm DOI: http://dx.doi.org/10.4251/wjgo.v8.i4.380

INTRODUCTION

Rationale for targeting inflammation in pancreatic cancer

Inflammation is a hallmark of cancer[1]. For over 100 years scientists have been interested in the relationship between inflammation and cancer. Researchers within Glasgow Royal Infirmary have for some time been interested in the relationship between cachexia, inflammation and poor prognosis in cancers of different origins. The modified Glasgow Prognostic Score (mGPS) that assesses blood albumin in combination with inflammation, C-reactive protein (CRP), has for over a decade been used to accurately predict outcome across a range of tumor types. Raised mGPS correlates with poor patient prognosis in colorectal, renal and pancreatic cancers[2]. Additionally, large observational studies have analyzed both cancer incidence and outcome based on daily aspirin use during previously performed randomized controlled trials. The long-term use of aspirin, a non-selective COX inhibitor, improves survival from cancer as a result of reduction in cancer incidence and metastatic burden[3-5]. These findings demonstrate a clear link between inflammation and cancer initiation and behaviour. Thus, there is observational evidence that inflammation promotes incidence, enhances progression and impacts on prognosis in patients with cancer.

Pancreatic adenocarcinoma (PDAC) presents at a late stage of progression and is associated with very poor outcomes (www.cancerresearchuk.org/cancer-info/cancerstats/). Surgery remains the only potentially curative treatment, though as few as 15% of patients have disease amenable to surgical intervention, and despite surgery the majority of these patients will succumb to recurrent disease. Therefore, new therapies and methods of instituting these therapies are required if survival is to improve in PDAC.

In addition to standard clinicopathological features, presence of systemic inflammation, as assessed by CRP, is a poor prognostic factor in patients undergoing surgical resection for PDAC. In a cohort of 135 patients who underwent potentially curative Whipple's resection for PDAC an elevated mGPS was independently associated with lower overall survival[6]. Furthermore a high neutrophil to lymphocyte ratio (NLR), a further index of host innate response, has been categorically shown to confer poor prognosis in PDAC[7]. Interestingly, in this study of 74 patients, NLR had improved utility at predicting disease recurrence than CRP. This phenomenon was not confined to resectable cases of PDAC, inoperable cases of PDAC appear to respond poorly to chemotherapy in the presence of a raised NLR[8]. Indeed in the randomized controlled clinical trial of nab-paclitaxel in PDAC an elevated NLR conferred poor prognosis in both treatment arms[9]. Therefore, assessment of host inflammation at the time of diagnosis of PDAC, has clinical implications for patient survival regardless of therapeutic modality.

The treating physician should consider the inflammatory insults they are subjecting patients to during their treatment course. Over the last decade minimally invasive surgery of the pancreas has increased significantly. When 65033 resections of liver and pancreas were assessed, patients who had minimally invasive pancreatic resections had reduced morbidity, mortality, and length of stay in hospital compared with those having open resections. Traditionally inflammatory insults generated by minimally invasive surgery are smaller than open procedures, however, at present, studies show no oncological benefit[10]. Intra-operative blood transfusion is associated with loss of immune surveillance in cancer patients, with associated increases in morbidity and mortality following surgery. These data suggest transfusion should be avoided in the peri-operative period if possible[11]. Furthermore, a profoundly elevated systemic inflammatory response in the post-operative period has been associated with increasing rates of infectious complications following a number of operations including pancreatectomy[12]. To our knowledge no randomized controlled data exist to confirm the findings of this meta-analysis, however, the study raises the question of the benefits of use of anti-inflammatories in the post-operative setting. Such benefits would have to be offset against potential increases in the risk of anastomotic leak. Thus, when dealing with the small percentage of patients who have PDAC suitable for operative management, surgeons must consider the implications of their treatments. Limiting inflammatory insults involved seems sensible but requires clarification *via* clinical trial.

In vivo models of PDAC

Preclinical studies in PDAC have improved greatly in the past decade with the development of murine models that genetically and histologically recapitulate the human disease. Murine models use pancreas specific promoters to drive oncogenic *Kras* and tumor suppressor gene mutations including mutant *Tp53* to create experimental PDAC murine models with an active microenvironment. These models permit preclinical interrogation of targeted therapies in the hope of translation to patients *via* clinical trial.

Importantly, progression of murine models of PDAC based on initiating oncogenic *Kras* mutations are greatly accelerated in the presence of pancreatic specific inflammation[13]. Further work by the same authors

revealed this was due to the requirement of pancreatitis to overcome oncogene-induced senescence, which can be blocked by anti-inflammatory medication[14]. Lee *et al*[15] found that when Kras was mutated within the pancreas, pancreatic inflammation led to reduction in *Ink4a* expression. Low levels of Ink4a allowed tumor cells to escape senescence and progress to form tumors. In the presence of Kras mutations, pancreatic inflammation is sufficient to induce tumor formation.

Following initiation of PDAC, inflammation promotes tumor progression. Within the tumor microenvironment there are many pro and anti-tumoral interactions[16]. Immune cells present have plasticity that permits differing both pro or anti-tumorigenic actions based on received stimulus. Ultimately, during PDAC evolution, a myriad of stromal elements, immune cells and key transducers of inflammatory signals cooperate to permit disease progression. Improvements in understanding the tumor microenvironment are permitting trial of novel therapeutics against key disease progression mediators. Ongoing research in this area will elucidate more completely the complex interactions within the tumor microenvironment and help future development and assessment of multi-target drug regimens.

DISCUSSION

Inflammatory targets identified by in vivo modeling studies in PDAC

Possible inflammatory therapeutic targets in PDAC can be classified into one of three categories: (1) immune modulation to target tumors; (2) targeting tumor stroma; (3) targeting signal transduction (Table 1).

This review will consider the progress made by preclinical studies in each of these three areas and how better understanding of the PDAC microenvironment has potential to translate to the clinical arena. Figure 1 provides a summary of potential inflammatory targets for therapy in PDAC.

Immune modulation

Tumor immunosurveillance is a term that refers to identification and clearance of tumor cells in the early stages of tumorigenesis by the adaptive immune system. It is the role of $CD8^+$ T cells to provide cytotoxic protection against "foreign" tumor cells, and hence the development of tumor immunogenicity. Different facets of immunosurveillance are now being interrogated to establish how PDAC so effectively evades detection.

Dendritic cells are a good example of an immune cell capable of adopting dual roles within the PDAC microenvironment. Dendritic cells can engage both $CD8^+$ and $CD4^+$ T cell responses dependent on stimulus[17]. Chemokine CXCL17 may be important for migration of dendritic cells to tumor sites while ICAM 2 upregulation was necessary for activation of a CD8+ cytotoxic response against tumor cells. Downregulation of CXCL17 and ICAM2 by tumor cells during evolution from precursor lesions to PDAC allowed tumors to develop immune tolerance[18]. In contrast Ochi *et al*[19] have demonstrated that blockade of TLR4 signaling promotes $CD4^+$ T helper cell activity which has a positive effect on pancreatic tumourigenesis through mediation of pro-tumorigenic inflammatory responses. The plasticity of the immune system was highlighted by the findings of Beatty *et al*[20]. In patients with metastatic PDAC, targeting CD40 with monoclonal antibodies led to tumor regression. Authors anticipated CD40 ligation would result in enhanced anti-tumoral T cell responses, however in fact resulted in anti-tumoral effects through macrophage infiltration. This phase 1 trial holds promise for trials of similar agents to activate an anti-tumoral immune response.

Tumor-associated macrophages (TAMs) are ever present from pre-invasive Pan-Ins to established PDAC[21]. TAMs exhibit an M2 phenotype that is pro-tumorigenic while suppressing adaptive immunity[22]. In cancer, signals received by macrophages from tumor cells including interleukin (IL)-10 and transforming growth factor (TGF)-β lead to adoption of an M2 phenotype[22]. Macrophages are attracted to the tumor microenvironment *via* production of chemokines by tumor cells[23]. CSF1 and CCL2 are crucial mediators of this chemo-attraction. CCL2 overexpression mediates migration of M2 macrophages to PDAC and is thought to play a key role in recruiting pro-tumourigenic macrophages to metastatic sites in development of the metastatic niche[24,25]. *In vivo* studies of anti-CCL2 drugs were effective in enhancing tumor immunity and impacting on metastasis in PDAC[26]. In addition, patients with high CCL2 expression and low CD8 T cell infiltration suffer poor outcomes following tumor resection.

Direct depletion of TAMs may also be a therapeutic option. Trabectedin has recently been licenced for study in PDAC and is currently in phase 2 trials in advanced disease (NCT01339754). Trabectedin can actively target macrophages *via* caspase-8 dependent apoptosis with selectivity to TAMs achieved through differential expression of TRAIL receptors by macrophages[27].

Promotion of anti-tumoral cell mediated responses has been successful, particularly in metastatic melanoma. These strategies focus on engaging T cell responses. CTLA4 inhibitor, ipilimumab, was the first drug shown to improve outcome in patients with metastatic melanoma. Following this development and success of Programmed cell death 1 (PD1)/Programmed cell death ligand (PDL1) T cell checkpoint inhibitors has led to great excitement in the field of oncology. These drugs have made a significant impact on survival of patients with metastatic melanoma. CTLA4 is a cell surface protein that suppresses T cell function. When drugs such as Ipilimumab bind CTLA4, T cell function is activated. Likewise, PD1 inhibits T cell function. Production of PD1s major ligand PDL1 by tumor cells and pro-tumorigenic immune cells permits tumors to escape T cell mediated adaptive immunosurveillance[28]. Hence PD1 is an ideal target when attempting to generate anti-tumoral immune responses.

Concerns exist that PDAC may not respond to such

Table 1 Preclinical assessment of inflammatory targets in pancreatic adenocarcinoma

Target	Drug	PMID	Year	Authors summaries
Hedgehog acyltransferase (Hhat)	RU-SKI 43	24469057	2015	*In vivo* mouse study targeting Hedgehog acyltransferase (Hhat). A lentivirally delivered hairpin RNA impeded the proliferation of pancreatic cancer *in vitro* and *in vivo*
Hedgehog	GDC-0449	25679326	2015	Combination therapy with GDC-0449 or miR-let7b *vs* single agent therapy effectively inhibited tumor growth when injected to athymic nude mice bearing ectopic tumors generated using MIA PaCa-2 cells
Sonic hedgehog pathways	Ormeloxifene	25840985	2015	Ormeloxifene caused potent inhibition of the SHH signaling pathway *via* downregulation of SHH and its related important downstream targets. Ormeloxifene potentiated the antitumorigenic effect of gemcitabine by 75% in PDAC xenograft mice
Hedgehog pathway	MEDI-5304	24344235	2014	MEDI-5304 displayed robust pharmacodynamic effects in stromal cells that translated to antitumor efficacy as a single agent in an HT-29/MEF coimplantation model of paracrine hedgehog signaling. MEDI-5304 also improved responses to carboplatin in the HT-29/MEF model. The antibody, however, had no effect as a single agent or in combination with gemcitabine on the CSC frequency or growth of several primary pancreatic cancer explant models
Hedgehog	GDC-0449	25278454	2014	GDC-0449 for 3 wk leads to downmodulation of GLI1 and PTCH1, without significant changes in CSCs compared with baseline. GDC-0449 and gemcitabine were not superior to gemcitabine alone in the treatment of metastatic pancreatic cancer
Hedgehog pathway	Metformin	24692708	2014	*In vitro*, BxPC3 human pancreatic cancer cells were treated with metformin, and Sonic hedgehog (Shh) mRNA and protein levels were examined. Metformin reduces the expression of Shh in several cancer cell lines including pancreatic cancer cells
Hedgehog	Curcumin	23563640	2013	Curcumin can inhibit the proliferation of TGF-β1-stimulated PANC-1 cells, it can induce apoptosis, and reverse the EMT. The possible underlying molecular mechanisms are through inhibition of the Shh-GLI1 signaling pathway
COX 5-lipoxygenase (5-LOX)	Dietary licofelone	25906749	2015	*In vivo* mouse study of licofelone, an agent that targets both COX-2 and 5-LOX
LOX	Zileuton	25483364	2014	Zileuton suppressed the proliferation of SW1990 cells in a concentration- and time-dependent manner. In addition, zileuton induced SW1990 cells to undergo apoptosis and significantly decreased 5-LOX expression
STAT3	Thiosemicarbazones	25561562	2015	*In vitro* and *in vivo* iron-binding ligands inhibit constitutive and interleukin 6-induced activation of STAT3 signaling DFO, Dp44mT, and DpC significantly decreased constitutive phosphorylation of the STAT3 transcription factor at Tyr705 in the pancreatic cancer cell lines and when injected *in vivo*
STAT3	Aspirin metformin	26056043	2015	Metformin combined with aspirin significantly inhibited the phosphorylation of mTOR and STAT3, and induced apoptosis as measured by caspase-3 and PARP cleavage Taken together, the combination of metformin ad aspirin significantly inhibited pancreatic cancer cell growth *in vitro* and *in vivo*
JAK2 STAT3	MicroRNA (miR)-216a	25220761	2014	MiR-216a overexpression markedly inhibited the JAK2/STAT3 signaling pathway and xenograft tumor growth *in vivo*
ALK pathway including STAT3	Crizotinib	25193856	2014	Crizotinib strongly suppressed the growth and proliferation of pancreatic cancer cells in a dose-dependent manner. Crizotinib strongly inhibited the expression of activated ALK in pancreatic cancer cells, modulating its downstream mediators such as STAT3, AKT, and ERK
STAT3 NF-κB COX-2 EP4	Nexrutine	24520096	2014	Nexrutine treatment inhibited growth of pancreatic cancer cells through induction of apoptosis Reduced levels and activity of STAT3, NF-κB, and their crosstalk led to transcriptional suppression of COX-2 and subsequent decreased levels of prostaglandin E2 (PGE2) and PGF2. Nexrutine intervention reduced the levels of NF-κB, STAT3, and fibrosis *in vivo*. Expression of prostaglandin receptor EP4 that is known to play a role in fibrosis was significantly elevated in human pancreatic tumors. Dual inhibition of STAT3-NF-κB by Nexrutine may overcome problems associated with inhibition of either pathway
JAK/STAT Src/FAK	Guggulsterone	23920124	2013	*In vitro*, guggulsterone treatment decreased mucin MUC4 expression in Capan1 and CD18/HPAF cells through transcriptional regulation by inhibiting Jak/STAT pathway
Notch JAK2	GSI IX and AG-490	24293409	2014	Combinational treatment with anti-NOTCH and JAK/STAT drugs significantly attenuates tumor progression *in vivo* and suppresses conversion from acinar-ductal-metaplasia to PDAC

Outlines the significant interest shown by preclinical researchers in targeting inflammation in PDAC. Using the search criteria pancreatic cancer/pancreatic adenocarcinoma + hedgehog, JAK/STAT, LOX we identified preclinical studies that have attempted to assess therapeutics targeted against these important inflammatory mediators of PDAC progression in the past 2 years. We have included those published in journals with an impact factor > 5. PDAC: Pancreatic adenocarcinoma; PARP: Poly-ADP-ribose polymerase; JAK: Janus kinase; STAT: Signal transducer and activator of transcription.

T cell interference because they are extremely fibrotic and desmoplastic. As a result PDACs have a relative

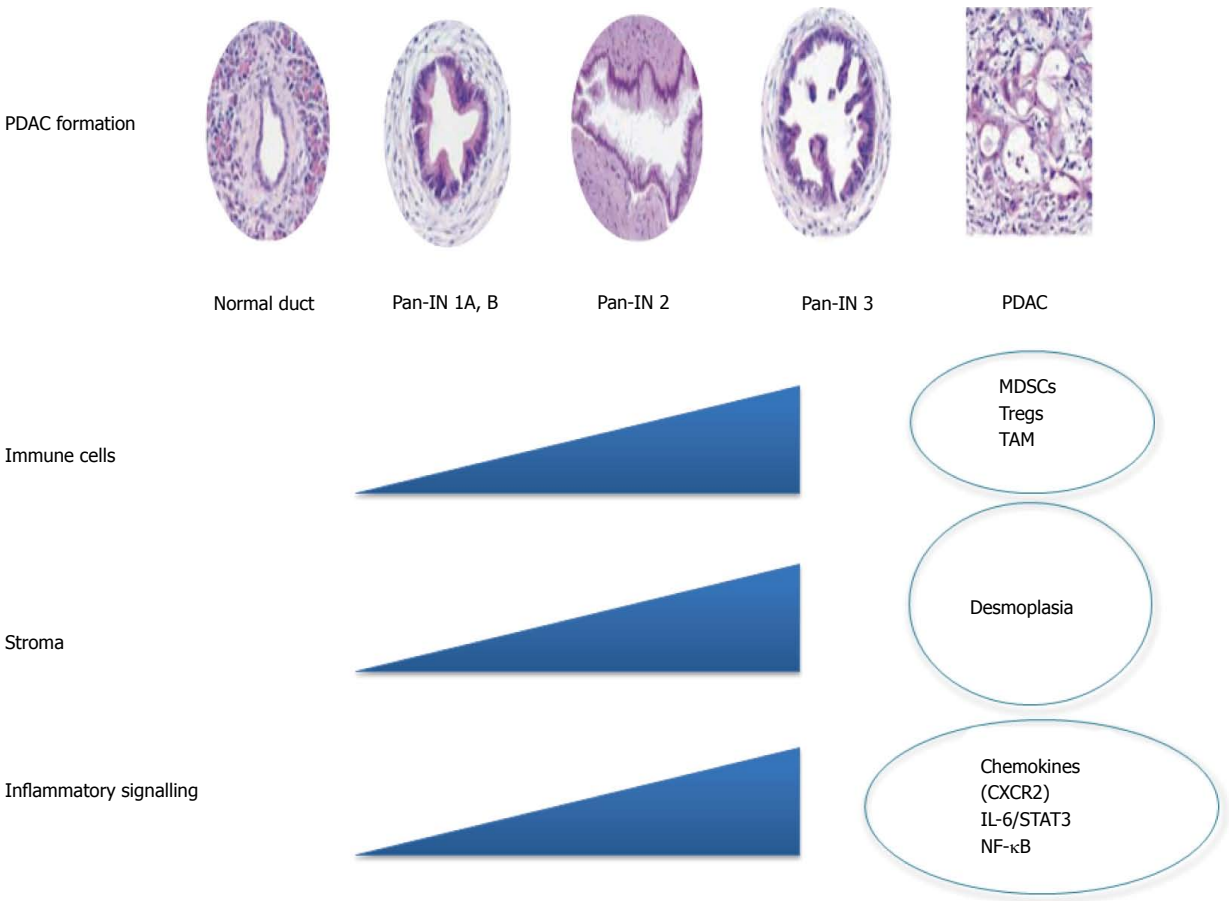

Figure 1 Changes in the pancreatic adenocarcinoma microenvironment during tumor formation. Pancreatic cancer forms from normal tissue *via* progression through pre-invasive pancreatic intra-epithelial neoplasia (Pan-IN) to invasive PDAC. Changes in immune cell components, stroma, and inflammatory signaling pathways all contribute to PDAC progression. Here we identify possible targets for therapy in PDAC. PDAC: Pancreatic adenocarcinoma; NF-κB: Nuclear facter kappa B; STAT: Signal transducer and sctivator of transcription; IL: Interleukin; MDSCs: Myeloid derived suppressor cells.

paucity of anti-tumoral T lymphocytes seen at histology compared with other epithelial tumors. Preliminary studies assessing ipilimumab have proven unsuccessful as a single agent[29]. Feig *et al*[30] have recently shown that immunosurveillance can be overcome in PDAC *in vivo* by expression of fibroblast activating protein (FAP) and production of CXCL12 by cancer associated fibroblasts (CAFs). These CAFs were able to prevent T cell infiltration to the tumor microenvironment. Interestingly when these CAFs were depleted genetically, or indeed CXCL12 was inhibited, tumors were sensitised to T cell checkpoint inhibition. Furthermore, myeloid derived suppressor cells (MDSCs) are orchestrated by PDAC to suppress proliferation and induce apoptosis in activated T cells[31]. Selective depletion of this granulocytic subset of MDSCs led to enhanced $CD8^+$ T cell responses promoting immunosurveillance. These data suggest that greater understanding of the processes of evasion of tumor immunosurveillance by PDAC will open up therapeutic opportunities *via* combination with therapies that enhance the effectiveness of immunogenics.

Tumor vaccines are designed to target tumor specific antigens, activating adaptive immunity, eradicating tumor cells. Studies have assessed PDAC specific antigens including MUC-1 that is expressed by over 90% of PDAC cells. Vaccine PANVAC-VF was developed to be active against cells expressing MUC-1, oncofetal protein carcinoembryonic antigen (CEA) and 3 co-stimulatory molecules. Unfortunately no survival benefit was seen with the addition of PANVAC-VF to standard therapy in a phase Ⅲ trial in palliative PDAC patients[32]. Ribonucleoprotein enzyme Telomerase, which maintains telomeric stability, has been assessed unsuccessfully as a potential vaccine target in the Telovac trial[33]. 1062 palliative patients were randomised to standard chemotherapy, sequential chemotherapy with Telovac or concurrent chemotherapy and Telovac. Neither Telovac groups showed any survival advantage. Smaller trials have been established against other targets including KRAS, although none has proven successful in clinical trial as yet showing how difficult it is to raise a successful adaptive immune response against PDAC.

Targeting tumor stroma

The majority of the tumor bulk of PDAC is composed of stromal cells. This dynamic network of immune cells, stellate cells and extracellular matrix is now believed to play a crucial role in sustenance and support for invasive tumor cells[34]. Stellate cells are key coordinators of fibrosis as a result of received signals from tumor cells in PDAC[35]. SPARC is one such factor present in high levels in the tumor microenvironment. SPARC functions

normally to promote wound healing, however its role in PDAC is less certain. High expression of SPARC is associated with poor patient survival in resected cohorts of PDAC patients[36]. Albumin-bound Paclitaxel (nab-paclitaxel) binds SPARC-expressing fibroblasts, allowing therapeutic targeting of this cell type. When nab-paclitaxel was combined with gemcitabine patients with metastatic PDAC survived significantly longer compared with standard gemcitabine chemotherapy[37]. Surprisingly no appreciable histological changes to the stroma were evident in the tumors of mice treated with nab-paclitaxel raising the possibility that targeting SPARC improved outcome *via* a different biological mechanism than predicted[38].

PDAC is desmoplastic, avascular and relatively acellular. These attributes are believed to be responsible for failure of chemotherapies to adequately access tumor cells. Recently, high tissue pressures within the PDAC stroma have been suggested to prevent chemotherapy delivery to tumor cells[31]. Preclinical model work has suggested relieving such pressures will enhance chemotherapy delivery and subsequent tumor cell death. Unfortunately, these findings have not translated to patients with drugs including anti-MMP and VEGF inhibitors failing to have a therapeutic effect in clinical trials[35]. Sonic hedgehog paracrine signaling through smoothened has been implicated in the coordination of stromal elements by tumor cells in PDAC. Despite this, a phase Ⅱ trial based on preclinical data assessing smoothened inhibition in PDAC was stopped early as patients receiving gemcitabine alone survived longer than those receiving the smoothened inhibitor in addition to gemcitabine[39] (clinicaltrials.gov, Infinity Pharmaceuticals, Cambridge, MA). In addition Catenacci *et al*[40] have recently found that Vismodegib, a Sonic hedgehog antagonist, when combined with gemcitabine provided no survival benefit in advanced PDAC patients than gemcitabine alone in a multicentre randomised controlled phase Ⅱ trial. Hyaluronan is a prominent element within the stroma of PDAC and when targeted in preclinical studies experimenters have found significant improvements in tumor vasculature and lowering of tissue pressures permitting access by chemotherapeutics[41,42]. This agent is currently the subject of phase Ⅱ clinical trials in combination with best current chemotherapeutic regimens FOLFIRINOX and gemcitabine/nab-paclitaxel (clinicaltrials.gov: NCT01959139 and NCT01839487).

At present no stromal agent is licenced for therapeutic use in PDAC, with sonic hedgehog in particular representing a cautionary tale of "bench to bedside" medicine. Recent studies, contrary to the findings of Olive *et al*[39], have proven that deletion of Shh specifically within the pancreas of *in vivo* PDAC models led to development of more aggressive tumors[43]. Furthermore, Özdemir *et al*[44] found eliminating CAFs from the tumor microenvironment led conversely to suppression of immunosurveillance, increasing numbers of T regulatory cells infiltrating the microenvironment, leading to tumor progression. What is clear from this work is that the PDAC stroma exists in a state of flux, with an interdependent network of stromal components which when manipulated therapeutically do not always produce expected results.

Targeting inflammatory signal transduction

Mutant *KRAS* is the major oncogenic driver of PDAC in more than 90% of cases[45]. Development of temporally controlled, inducible models of PDAC has recently permitted interrogation of signaling mechanisms required for PDAC tumorigenesis and progression. Use of inducible and reversible *Kras* alleles has demonstrated the requirement of ongoing stimulus from *Kras* for precursor lesions to progress to PDAC. Removal of *Kras* stimuli prevented progression from pan-INs to PDAC. However, when mutant *Kras* expression remained switched on, striking stimulation of the hedgehog signaling pathway was observed in addition to upregulation of inflammatory mediators IL-6, STAT3, and COX2. *Kras* inactivation resulted in decreased expression of these inflammatory mediators and resultant pan-IN regression[46], providing clear evidence of the relationship between *Kras* mutation and coordination of the inflammatory response in PDAC. KRAS activates RAF phosphorylation resulting in production of chemokines including CXCL1 and CXCL8[47]. CXCR2 a G-protein coupled receptor is crucial for MDSC migration to the tumor microenvironment and metastatic sites in breast and colon cancer and is activated by CXCL1, 2, 5, 7 and 8[48,49]. CXCR2 inhibition in preclinical models of PDAC successfully delayed tumor progression, suggesting it merits further study[50].

Ochi *et al*[51] recently reported high expression of TLR7 in PDAC. Activation of TLR7 promotes PDAC formation *via* downstream signalling through inflammatory signalling pathways including STAT3 and nuclear facter kappa B (NF-κB). When TLR7 was knocked out of immune cells within a murine model of PDAC and exposed to the same pro-tumorigenic conditions animals were completely protected from pancreatic carcinogenesis. Pharmacological TLR7 inhibition is yet to be assessed.

Transcription factor STAT3 represents a key-signaling node in PDAC[52,53]. When mouse models expressing endogenous mutant *Kras* combined with experimentally induced pancreatitis were assessed, STAT3 activation was significantly increased. Absence of *STAT3* from the pancreata of these mice led to a block in acinar to ductal metaplasia and pan-IN formation, while reduced immune cell infiltration and IL-6 expression was also observed. Infiltrating macrophages were identified as producing IL-6 leading to STAT3 upregulation. Corcoran *et al*[54] have proposed that patients could be selected to trial based on phosphoSTAT3 levels as they predict PDAC cell sensitivity to JAK/STAT inhibitors. As the Jak/STAT signaling cascade has been recognised to impact on survival following resection for PDAC, investigators are now beginning to target it in randomized controlled trials[55].

Ruxolitinib targets the IL6/JAK/STAT signaling cascade. Assessment *via* double blind randomised controlled trial in

advanced PDAC with capecitabine *vs* capecitabine/placebo showed a marginal survival advantage in the ruxolitinib group[56]. Intriguingly, those patients that benefited most were those with high mGPS scores. This work and that in preclinical studies by Corcoran *et al*[54] suggests trial of anti-inflammatory agents requires careful patient selection to optimise outcome in PDAC. Two ongoing phase Ⅲ trials of JAK/STAT inhibition in PDAC, JANUS 1 and 2, basing patient selection on high systemic inflammatory scores, will test the hypothesis of the need for better patient selection in PDAC trials of inflammatory targeted agents.

NF-κB is also important in PDAC progression downstream of Kras mutation, specifically IKK2/β releases NF-κB from inhibition leading to progression of pancreatitis, ductal metaplasia, PanIN formation and eventually PDAC formation[57]. Genetic inactivation of IKK2/β in preclinical PDAC models led to failure of mice to develop tumors, while IKK2/β deficient animals showed reductions in pancreatic cell proliferation rates and reduced inflammatory cell infiltrate. These observations support a critical role for NF-κB in PDAC tumorigenesis. Unfortunately NF-κB is difficult to pharmacologically target effectively due to the complexity of regulation within the signaling cascade. Inhibitors of IKK2/β have so far failed to reach clinical trial.

SUMMARY

Preclinical trials are beginning to inform us as to tumor generated and tumor associated inflammation, how these factors help progress PDAC, and how they may be countered therapeutically.

Robust murine models of human disease now exist to allow preclinical trial of therapeutic agents. From these models researchers have established MDSCs, CAFs and TAMs are key cellular mediators of immunosuppression. Targeting these cells may sensitise tumors to immunotherapies such as anti-PD1 and CTLA4 antibodies. Immunotherapies have been extremely successful in diseases such as metastatic melanoma and if tumors can be "unmasked" from immunosuppressive elements this strategy is an exciting prospect in PDAC. IL-6/STAT3 and NF-κB represent established inflammatory signaling nodes that progress PDAC. Trial of JAK/STAT inhibition shows early promise in clinical trial. However, NF-κB remains an extremely difficult target to develop drugs against.

Early trials with trabectedin (immune cells), targeting hyaluronan (tumor stroma), and JAK/STAT inhibitors (inflammatory signaling), are extremely promising, however, as yet no large randomised controlled phase Ⅲ trials have been published.

In future, we envisage combination trials targeting all three aspects of the pro-tumoral PDAC microenvironment will lead to better results in carefully selected patients. Pre-clinical assessment of such strategies is already under trial in robust mouse models of PDAC. A number of inflammatory targets, as outlined in this commentary, have been identified for trial, therefore the next decade of randomised controlled clinical trial data will determine the effectiveness of agents against these key inflammatory mediators in PDAC.

It is important to note the relative lack of success of translation of stromal/inflammation targeting therapies to clinical trial from the laboratory at present. Only those therapies that demonstrate the most robust preclinical data should be taken forward. Patient selection for tumor microenvironment targeted therapies is a key issue, as is identification of biomarkers of response to such therapies. While those patients presenting with high levels of inflammation are easy to identify clinically, objective monitoring of response to therapy is more difficult due to the lack of robust biomarkers and paucity of available tissue to assess response. Strategies that incorporate pre and post-treatment endoscopic ultrasound biopsies must be considered to help develop techniques required to run robust clinical trials. Immune cell profiling could be employed to stratify subgroups of resected PDACs, potentially enabling individualized targeted immunotherapeutic strategies.

In PDAC the multitude of pathways and factors that determine progression remains the main obstacle in combating this aggressive disease. It is probable that to generate durable responses, in such a plastic disease as PDAC, carefully selected combination therapies will be required. Such strategies are likely to evolve to incorporate chemotherapeutics, immunogenics and therapies targeted against tumor stroma and signal transduction. The recent steady progression made in advanced PDAC with FOLFIRINOX and nab-paclitaxel will hopefully progress further with complementary therapeutics targeted against these different components of the tumor microenvironment.

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P- Reviewer: Bilir C, Kang CM, Kleeff J, Nagahara H, Sperti C
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Lu YJ

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