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A new scalpel for the treatment of pancreatic cancer: Targeting stromal-derived STAT3 signaling

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Currently, the prognosis for patients with pancreatic ductal adenocarcinoma (PDAC) is poor, with a five-year survival rate of only 6% in the United States.[1] This dismal prognosis is due in part to a majority of patients presenting with locally advanced or metastatic disease at diagnosis, and the limited number of effective treatment options available. PDAC is an infiltrating malignancy of the exocrine pancreas that features a robust and heterogeneous desmoplastic stromal response. The stroma often comprises a majority of the tumor volume and consists of extracellular matrix, blood and lymphatic vessels, and multiple other cell types including fibroblasts, pancreatic stellate cells, macrophages, and other immune cells. Although some elements of the stroma may serve to protect cancer cells from cytotoxic chemotherapy,[2] other aspects may restrain the tumor and prevent a more aggressive phenotype. [3, 4] In addition, there is a growing recognition of the impact of stromal-epithelial interactions in modulating the effects of chemotherapy. Therefore the stroma represents a complicated entity that cannot be viewed as a monolith that performs pro-tumor and pro-metastatic roles as previously thought. Indeed, cancer biologists have been humbled by the recent failed clinical trial of IPI-926, an agent that inhibits canonical Hedgehog signaling, one of the major drivers of the PDAC desmoplastic response, despite promising preclinical data. Thus, strategies to deplete or target desmoplasia must be considered carefully, as our understanding of stromal-epithelial interactions continues to evolve. In this issue of *Gastroenterology*, Nagathihalli *et al.* demonstrate that gemcitabine (Gem) and inhibition of signal transducer and activator of transcription 3 (STAT3) synergizes to remodel, rather than deplete, PDAC-associated desomplasia, thereby enhancing drug delivery and therapeutic response in mouse models of pancreatic cancer.[5] Their results underscore the importance of STAT3 signaling in shaping the PDAC tumor microenvironment and provide additional evidence to suggest that targeted manipulation of the tumor microenvironment can indeed improve drug delivery, without negating the beneficial effects the stroma has on constraining the tumor.

The STAT family of proteins is classically activated through tyrosine phosphorylation by the Janus family kinases (JAKs) upon binding of cytokines and growth factors to their receptors.

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Phosphorylated STAT proteins subsequently dimerize and translocate to the nucleus where they act as transcription factors. Of the seven STAT proteins, STAT3 has emerged as an important signaling intermediate in the development and progression of pancreatic cancer. Activated STAT3 is increased in PDAC ductal cells compared to non-transformed ducts,[6] and deletion or inactivation of Stat3 in mouse models of pancreatic cancer impairs *Kras*^{G12D}-driven PDAC progression.[7–9] Importantly, elevated expression of activated (phosphorylated) STAT3 is associated with poor prognosis in patients with early stage PDAC undergoing pancreatic resection.[10] Nagathihalli *et al.* extend this association by evaluating a tissue microarray of patient samples for the presence of STAT3. Interestingly, in addition to phosphorylated STAT3 (pSTAT3), the authors identified an increase in total STAT3 expression itself with progression of disease. Moreover, patients with elevated pSTAT3 had increased tumor grade and reduced overall survival when compared to those patients with lower pSTAT3 expression. At the cellular level, STAT3 activation is associated with proliferation, inhibition of apoptosis, invasion, and motility of pancreatic cancer cells.[6, 11–13] In PDAC, STAT3 activation is largely a result of interleukin 6 (IL6) signaling from the tumor microenvironment,[7, 9, 14] demonstrating a classical pro-tumorigenic axis derived from the stroma.

Surprisingly, in addition to supporting PDAC progression, STAT3 may also contribute to resistance to cytotoxic chemotherapy. To inhibit STAT3 activation, the authors employed a JAK2 inhibitor, AZD1480, which was previously reported to robustly suppress STAT3 activation.[15] The authors administered AZD1480 and Gem, alone or in combination, in xenograft and autochthonous mouse models of PDAC, with striking results. Inhibition of STAT3 signaling led to decreased PDAC cell expression of cytidine deaminase, an enzyme responsible for metabolizing gemcitabine to an inactive intermediate. In addition, STAT3 inhibition decreased expression of the matrix protein, secreted protein, acidic, cysteine-rich (SPARC). Interestingly, SPARC has been shown to directly inhibit migration and proliferation of endothelial cells and may contribute to hypoperfusion and poor drug delivery reported in PDAC. Indeed, the authors observed a significant increase in vascular density in xenografted tumors treated with AZD1480 plus Gem compared to Gem monotherapy or control mice. These changes related to significantly enhanced delivery of gemcitabine to xenografts. In addition to SPARC, combination Gem plus AZD1480 altered additional tumor matrix components; combination therapy, but not monotherapy, resulted in increased collagen fiber disorganization, with increased variation in fiber direction and decreased parallel fiber alignment. No changes in inflammatory cells or myofibroblasts were noted between treatment groups, suggesting that STAT3 inhibition-induced stromal remodeling spared key cellular components.

Collectively, the work by Nagathihalli *et al.* demonstrates how a detailed understanding of Kras-driven desmoplasia can shed light on potentially novel strategies for the treatment of PDAC. Specifically, the authors identify two novel ways in which the stroma, directly or indirectly, may compromise the effects of cytotoxic chemotherapy. Although effective at inducing cell death *in vitro*, the clinical benefit of gemcitabine monotherapy for patients with advanced PDAC leads to a median overall survival rate of 5–6 months, and it has largely been supplanted by more recent combination regimens.[16] One potential reason for reduced efficacy of gemcitabine *in vivo* is suboptimal delivery of drug to the tumor itself.

Thus, if drug delivery can be improved, the efficacy of the drug is increased.[2] Indeed, inhibition of STAT3 signaling, triggered by stromal-derived IL6, resulted in increased microvascular density and drug delivery through effects on SPARC production. Gemcitabine resistance can also arise through efficient metabolism of the drug itself into inactive components by enzymes such as cytidine deaminase. Interestingly, STAT3 inhibition reduced expression of cytidine deaminase. Thus, Nagathihalli *et al.* identify a novel strategy to target the stroma in a highly targeted manner, resulting in dramatic results in preclinical models of PDAC. Indeed, other combination therapies are finding success in targeting the tumor stroma, including *nab*-paclitaxel, an albumin-bound formulation of paclitaxel, which increases tumor vascularization and enhances delivery of gemcitabine, potentially through its association with SPARC expressed in the stroma, though controversial.[17] Similarly, a combination of the vitamin D derivative, paracalcitriol, with gemcitabine and nab-paclitaxel has demonstrated considerable promise via stromal remodeling and improved efficacy in preclinical models[18], and is now undergoing clinical evaluation.

The relationship between the neoplastic cells and the stroma in PDAC is complex. Subtle changes in the stromal composition may produce drastic effects on the tumor biology, and therapeutics that target the PDAC stroma may produce unexpected results. However, we maintain that a better understanding of the functional roles of the desmoplastic stroma in PDAC will lead to new therapeutic strategies for this disease, in particular, attempts at remodeling the tumor-associated stroma back towards its normal self. In this regard, a recent large scale profiling study of PDAC molecular signatures has underscored the presence of stromal dichotomy, with both ‘active” and “normal” stromal gene signatures present across individual PDAC[19]; not surprisingly, PDAC with preponderance of ‘active” stromal signature harbor an adverse prognosis, reiterating the importance of recalibration towards “normal”. Further, recent promising data from preclinical models and a clinical trial support this idea after recent unexpected failures in the clinic (Table 1). Given the results presented by Nagathihalli *et al.*, as well as work by others, the therapeutic inhibition of STAT3 activation in PDAC warrants further investigation.

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Table 1

Summary of selected preclinical and clinical data investigating the potential of targeting tumor stroma to improve therapeutic response

Target	Summary	Reference
Hedgehog (Hh) signaling	Therapeutic inhibition of Hh signaling using IPI-926 depleted stroma, increased vasculature and drug delivery of gemcitabine, and extended survival in mouse models	Olive *et al.*[2]
Hh signaling	Phase II clinical trial of Gem plus either IPI-926 or placebo halted after preliminary analysis of data showed a higher rate of progressive disease with IPI-926 compared to placebo group, as well as shortened overall survival	Infinity Pharmaceuticals[20]
Hh signaling	Pancreas-specific deletion of sonic hedgehog in a genetic mouse model depleted stroma and accelerated progression of pancreatic cancer	Rhim *et al.*[4] Ozdemir *et al.* [3] Lee *et al.* [21]
Vascular endothelial growth factor A (VEGF-A)	Phase III clinical trial of bevacizumab (a recombinant monoclonal antibody against VEGF-A) in combination with Gem showed no survival advantage compared to Gem plus placebo	Kindler *et al.*[22]
CD40	Therapeutic activation of CD40 with monoclonal antibody agonists induced tumor regression by stimulating macrophages to infiltrate the tumor	Beatty *et al.*[23]
Hyaluronan	Therapeutic ablation of stromal hyaluronan with PEGPH20, a hyaluronidase, in a mouse model normalized interstitial fluid pressures and expanded the microvasculature, thereby increasing perfusion of Gem and improving response	Provenzano *et al.*[24]
Cell-matrix interactions	*nab*-Paclitaxel decreases cytidine deaminase expression, increases intratumoral Gem levels, reduces metastatic burden, and causes tumor regression in mouse models	Frese *et al.*[25]
Cell-matrix interactions	*nab*-Paclitaxel plus Gem significantly improves median overall survival, progression-free survival, and response rate compared to Gem alone in phase III clinical trial of patients with advanced PDAC	Von Hoff *et al.*[17]
Fibroblast activation protein (FAP)-expressing stromal cells	Adoptive transfer of FAP-targeted chimeric antigen receptor T cells significantly inhibited tumor growth in mouse models	Lo et al.[26]
Chemokine (C-X-C motif) ligand 12 (CXCL12)	Inhibiting the receptor for CXCL12, a chemokine produced by FAP-positive cancer-associated fibroblasts in the stroma, promoted T cell accumulation and, in combination with an immune checkpoint antagonist, reduced tumor volume	Feig *et al.*[27]
Connective tissue growth factor (CTGF)	Antagonism of CTGF with the FG-3019 monoclonal antibody in combination with Gem increased apoptosis in neoplastic cells without disrupting the stroma	Neesse *et al.*[28]
Vitamin D receptor (VDR)	Stimulation of VDR with a vitamin D analog induced quiescent state of pancreatic stellate cells, thereby suppressing pro-tumorigenic signaling and enhancing Gem-mediated response	Sherman *et al.*[18]