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Road Map to Defeat Pancreatic Cancer

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Keywords

pancreatic cancer, KRAS, metastasis, stroma, inflammation, metabolism

Abstract

Pancreatic cancer is a notoriously deadly disease characterized by many challenges in clinical management. Despite important advances in our understanding of pancreatic cancer progression and its underlying molecular biology over the last decades, there is a long road ahead if we aim to meaningfully improve patient outcomes in this difficult disease. Treatment options remain limited, and patient prognosis, although improving, remains bleak. As we build toward the future, we propose a framework for targeting the seven deadly hallmarks of pancreatic cancer in an effort to cure this disease. The high mortality and aggressive nature of pancreatic cancer can be largely ascribed to (*a*) diagnostic deficiencies, (*b*) chronic inflammation, (*c*) desmoplastic stroma, (*d*) early metastasis, (*e*) KRAS signaling, (*f*) metabolism, and (*g*) rapid deconditioning. Here, we outline the challenges presented by each of these disease hallmarks and highlight ongoing research to tackle each one.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC; pancreatic cancer) is a notoriously deadly disease, and it accounts for the vast majority of all pancreatic cancers each year. Despite constituting only 3.3% of cancer cases annually, pancreatic cancer is the third leading cause of cancer-related death in the United States and one of a few cancers for which incidence is increasing (Siegel et al. 2024). The strikingly high mortality in this disease can be attributed to several clinical features: characteristically late diagnosis, broad resistance to targeted and cytotoxic therapies, and aggressive metastasis. Clinical symptoms preceding PDAC are often vague, and a vast majority of patients will be diagnosed with treatment-refractory systemic disease that is ineligible for surgical resection, still considered the only potentially curative therapy. Together, these factors contribute to a 5-year survival rate of only 13% (Siegel et al. 2024). Although this number demonstrates the significant challenges that remain to improve patient outcomes, it also signifies the progress made in the past two decades to bring the 5-year survival rate up from below 7%.

Thanks to significant efforts in the field, a detailed molecular understanding of PDAC progression has emerged. We understand the genetic drivers underlying both heritable and sporadic pancreatic cancer, as well as core signaling pathways that are dysregulated in cancer progression (Hayashi et al. 2021, Klein 2021). Although we have long understood that pancreatic cancer is largely characterized by mutations in *KRAS2*, *TP53*, *CDKN2A*, and *SMAD4* (Hayashi et al. 2021), evolutionary analysis has revealed that *KRAS* mutations are common in early benign pancreatic lesions such as pancreatic intraepithelial neoplasia (PanIN) and cystic intraductal papillary mucinous neoplasms (Singhi & Wood 2021). Further, low-grade PanINs, the most common PDAC precursor, are present almost universally in healthy adults (Carpenter et al. 2023, Singhi & Wood 2021); thus, the uncommon development of invasive cancer must require cooperation between oncogenic mutations and environmental insults. Our deeper molecular understanding of PDAC has also advanced the development of important preclinical tools, including genetically engineered mouse models (GEMMs) (Westphalen & Olive 2012), patient-derived organoids (PDOs) (Boj et al. 2015), and tissue explant culture models (Decker-Farrell et al. 2023). GEMMs have facilitated a range of discoveries, from the role of the tumor stroma in disease progression to the development of pancreatic cancer from diverse cells of origin, including nonductal acinar cells of the pancreas (Westphalen & Olive 2012). Meanwhile, organoid and explant models better represent patient heterogeneity and allow the rapid interrogation of patient tumor biology both in vivo and in vitro.

Despite advances in our understanding of pancreatic cancer progression and its underlying molecular biology, there is still a long road ahead if we aim to meaningfully improve patient outcomes in this challenging disease. Treatment options remain limited, and patient prognosis, although improving, remains bleak. As we build toward the future, we propose a framework for targeting the seven deadly hallmarks of pancreatic cancer in an effort to cure this disease (**Figure 1**). The high mortality and aggressive nature of pancreatic cancer can be largely ascribed to (*a*) diagnostic deficiencies, (*b*) chronic inflammation, (*c*) desmoplastic stroma, (*d*) early metastasis, (*e*) KRAS signaling, (*f*) metabolism, and (*g*) rapid deconditioning. Here, we outline the challenges presented by each of these disease hallmarks and highlight ongoing research to tackle each one.

ADDRESSING DIAGNOSTIC DEFICIENCIES

One of the toughest challenges in pancreatic cancer is our inability to diagnose disease before it progresses to an advanced stage. There is currently no effective noninvasive method for early PDAC diagnosis in the general population, and only ~15% of patients are diagnosed with local

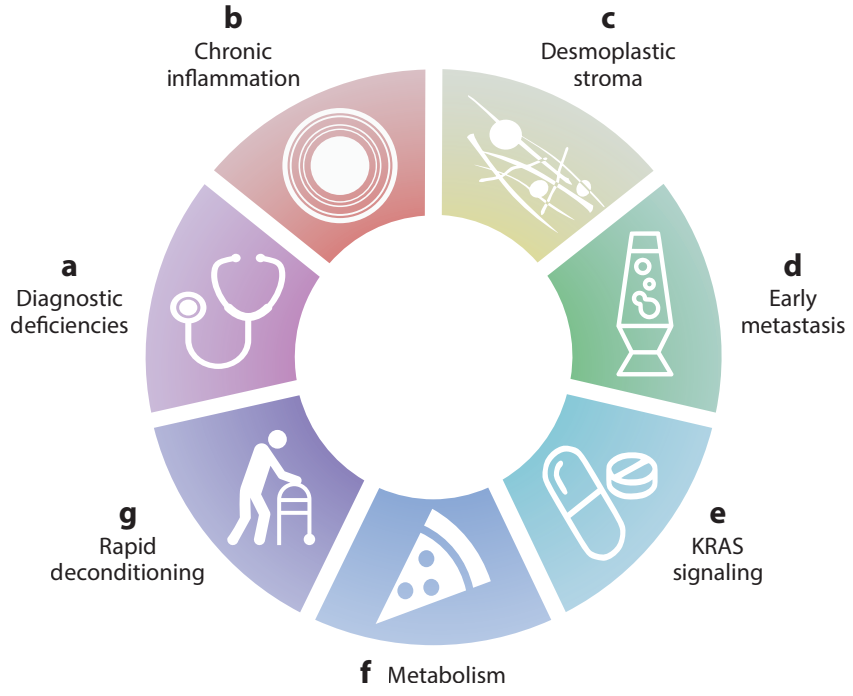

Figure 1

Seven deadly hallmarks of pancreatic cancer. The high mortality and aggressive nature of pancreatic cancer [pancreatic ductal adenocarcinoma (PDAC)] can be largely ascribed to seven major features. In order to improve patient prognosis and strive toward a cure for PDAC, we will need to overcome each of these challenges. (*a*) Diagnostic deficiencies. There is currently no method for PDAC diagnosis in the general population, leading to late-stage detection of systemic disease that is difficult to manage clinically. (*b*) Chronic inflammation. Inflammation caused by PDAC risk factors fuels tumorigenesis and immunosuppression and is therefore an important target for prevention and therapy. (*c*) Desmoplastic stroma. A prominent fibrotic reaction is a defining feature of PDAC that should be addressed to improve therapy response and block tumor progression. (*d*) Early metastasis. Early and aggressive metastasis is a significant cause of PDAC mortality; intercepting disease progression and metastatic spread could benefit patients. (*e*) KRAS signaling. Mutant KRAS is the central oncogenic driver of PDAC; new clinical KRAS inhibitors have the potential to transform PDAC therapy and shift our focus to emerging resistance mechanisms. (*f*) Metabolism. Dysregulated metabolism is crucial for PDAC cell fate and survival in the harsh tumor environment and could provide important avenues for therapy. (*g*) Rapid deconditioning. Late-stage diagnosis leads to rapid physiological decline in patients, emphasizing the importance of precision medicine approaches to improve patient responses to therapy.

disease amenable to surgical resection (Siegel et al. 2024). These patients have much higher survival rates, indicating that improved early-stage diagnosis could greatly benefit patients (Park et al. 2021). However, diagnostic development has been hampered by low disease prevalence in the general population. Lifetime PDAC risk is as low as ~1% (Park et al. 2021), meaning that even a test with 99% accuracy would generate a large number of false positives and risk medical overtreatment. To address this problem, it is necessary to define high-risk patient groups that could benefit from screening. Recently, the Cancer of the Pancreas Screening Study (CAPS) used familial history and/or cancer-associated genetic variants to identify high-risk patients for enrollment in endoscopic ultrasound imaging–based surveillance; this resulted in earlier-stage detection and improved survival, affirming the benefit of sophisticated screening modalities for

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high-risk groups (Dbouk et al. 2022, Goggins et al. 2020). Despite the success of this approach, CAPS focuses on patients with the highest heritable PDAC risk. In the future, it will be crucial to model risk based on combined genetic and nongenetic features to comprehensively identify patient groups at risk of sporadic PDAC that could benefit from screening. Patients with new-onset diabetes (NOD) may be one such group. NOD can be a harbinger of cancer, and work is ongoing to establish a prospective NOD cohort as a platform to develop biomarkers and surveillance protocols (Maitra et al. 2018, Stoffel et al. 2023). In fact, it is becoming increasingly clear that clinical signs such as hyperglycemia (Sharma et al. 2018) and unexplained weight loss (Babic et al. 2023) can precede diagnosis by several years. In an effort to parse these clinical indicators, machine learning has been used to develop models to predict PDAC risk based on hospital disease codes over time (Placido et al. 2023). Although this type of strategy requires optimization, it could be a promising route for risk assessment, especially if we incorporate quantitative clinical datasets.

In addition to refining risk stratification, research should continue to focus on designing noninvasive, cost-effective, and specific tests that are reasonable to apply to more moderate-risk groups. Currently, imaging remains the best diagnostic for PDAC; however, current imaging modalities such as endoscopic ultrasound can be expensive and invasive and have limited ability to detect small lesions. PanINs cannot be detected at all by current techniques, and although cystic precursors may be visible, it is often unclear which cysts warrant intervention (Stoffel et al. 2023). Some efforts have focused on training artificial intelligence to improve the sensitivity of current imaging modalities (Cao et al. 2023); however, work to improve diagnostics largely aims to devise alternative imaging strategies or identify biomarkers that could supplement or reduce the need for imaging (England et al. 2016). In our own work, we have used an epitomics approach to generate antibodies for immuno-imaging of pancreatic tumors (Oni et al. 2020a). Using membrane protein fractions derived from PDOs, we immunized rats and generated tumor-specific CEACAM6-reactive monoclonal antibodies. When radio-labeled, these antibodies specifically detected pancreatic tumors in transplant models. Although further evaluation is required, these results suggest that an immuno-imaging strategy could have clinical utility in PDAC detection. Similar immuno-imaging approaches have been developed to target tumor-enriched biomarkers including mesothelin, mucins, and proteins bearing the glycoprotein CA19-9, although only CA19-9 imaging probes have been investigated clinically (González-Gómez et al. 2021, Lohrmann et al. 2019).

In parallel, putative PDAC biomarkers are being investigated in a wide range of biological sources including blood, stool, saliva, and pancreatic and cystic fluid (Singhi & Wood 2021, Stoffel et al. 2023, Trikudanathan et al. 2021). These biomarkers are in varying stages of clinical development; however, CA19-9 remains the only biomarker with demonstrated clinical utility. CA19-9 is approved for evaluating therapy response in PDAC, but it is not sufficient for cancer detection (Stoffel et al. 2023). Nonetheless, CA19-9 may be an important benchmark and baseline tool with which other biomarkers are combined. Indeed, it seems likely that a biomarker panel rather than any singular marker will be required for an effective diagnostic test. Although clinical results are forthcoming, several multiparameter blood-based tests are under evaluation. These include two blood-based diagnostics: the IMMray PanCan-d test, an 8-plex antibody biomarker test (Brand et al. 2022), and CancerSEEK (Cohen et al. 2018), a polymerase chain reaction–based test to detect cancer-associated mutations in circulating tumor DNA (ctDNA). Detection strategies based on the methylation signatures of ctDNA are also in development (Guler et al. 2020, Liu et al. 2020); however, DNA-based methods face challenges in earlier disease, when DNA shed by small lesions is low. Extracellular vesicles shed into the circulation are often abundant and contain tumor-specific proteins that can be detected prior to the emergence of metastatic disease (Hoshino et al. 2020); although the diagnostic utility of this approach requires clinical development, it adds another putative biomarker to the growing arsenal. As we advance risk

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assessment in patients, these ever-improving tools may become an effective means of further stratifying high-risk individuals for enrollment in surveillance, and they could help direct clinical management of patients with precursors detected by imaging (Stoffel et al. 2023).

CHRONIC INFLAMMATION

As we have come to understand the environmental drivers of pancreatic cancer development, it has become clear that these factors converge on a central feature: inflammation. Elevated PDAC risk has been linked to pancreatitis, tobacco or alcohol consumption, diabetes, and obesity (Klein 2021, Stoffel et al. 2023); each of these risk factors is associated with chronic inflammation that is posited to promote tumorigenesis (Stone & Beatty 2019). Among these, pancreatitis is perhaps the most well characterized. Pancreatitis is most often modeled in mice by administering a synthetic cholecystokinin (CCK) analog called cerulein that stimulates pancreatic enzyme secretion and induces hallmarks of pancreatitis including reversible immune cell infiltration, metaplasia, and fibrosis (Saloman et al. 2019). Using this model, researchers have shown that pancreatitis potentiates *Kras*-driven tumorigenesis in adult acinar cells in mice (Friedlander et al. 2009, Guerra et al. 2007). Further studies in animal models have shown that tobacco use (Hermann et al. 2014, Wittel et al. 2006), alcohol consumption (Asahina et al. 2020), obesity (Eibl & Rozengurt 2021, Philip et al. 2013, Ruiz et al. 2023), and diabetes (Zhang et al. 2023) similarly induce local pancreatic inflammation that synergizes with mutant *Kras* ($Kras^{MUT}$) to drive proliferation and acinar-to-ductal metaplasia (ADM), fostering tumorigenesis. These results support a model in which convergent oncogenic and inflammatory insults are required for, or at least facilitate, tumorigenesis. This model is reinforced by the observation that low-grade *KRAS*-mutant PanINs are common in healthy adults (Carpenter et al. 2023); contrasting with the low prevalence of PDAC, this suggests that cooperation between mutant *KRAS* and environmental factors is required for tumorigenesis in humans. As a common feature of environmental PDAC risk, inflammation is therefore an important target for PDAC prevention. In practice, the clinical evaluation of prevention strategies is difficult and relies on effective selection of high-risk patients as outlined above. However, if attained, a preventative intervention offers the benefit of cutting off nascent precancer before it evolves greater complexity and resistance to therapy.

Efforts to identify mechanisms underlying inflammation-associated PDAC development have found that diverse inflammatory risk factors can support tumorigenesis through the activation of common effector pathways such as NFκB or STAT3, via cytokine signaling from infiltrating immune cells (Hausmann et al. 2014). Inflammation also convergently enables tumorigenesis through the amplification of Ras signaling. As mentioned, $Kras^{MUT}$ alone does not appear sufficient for PDAC initiation; however, inflammation in the context of $Kras^{MUT}$ boosts Ras activation above a critical threshold required for dedifferentiation and transformation (Daniluk et al. 2012, Eibl & Rozengurt 2021, Ji et al. 2009, Philip et al. 2013). Focusing specifically on models of pancreatitis, a series of recent studies have also elegantly illustrated the role of epigenetic reprogramming in coordinating acinar cell response to inflammatory cues and *Kras* mutation in mice (Alonso-Curbelo et al. 2021, Burdziak et al. 2023, Del Poggetto et al. 2021). Cytokine signals produced during pancreatitis mediated shifts in chromatin accessibility that were maintained in acinar cells over time, allowing them to access neoplasia-associated gene expression programs in the context of $Kras^{MUT}$. This work provides evidence that epigenetic dysregulation occurs early in PDAC progression in concert with inflammation and may be an important axis to target therapeutically. Toward developing an actionable target for pancreatitis, work in our own lab has shown that inducible production of the glycan biomarker CA19-9 is sufficient to drive pancreatitis and tumorigenesis in mice via EGFR hyperactivation (Engle et al. 2019). Treatment with a

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CA19-9 antibody reduced pancreatitis, indicating that this strategy could serve as a novel therapy for pancreatitis and possibly PDAC prevention. Whether both epigenetic dysregulation and CA19-9 play a central role in PDAC arising in other inflammatory contexts such as obesity remains to be seen. Indeed, there is evidence that tumorigenesis associated with metabolic syndrome is somewhat mechanistically distinct and closely tied to endocrine signaling (Eibl & Rozengurt 2021, Ruiz et al. 2023). Obesity-associated hyperinsulinemia can cause inflammation through insulin receptor signaling in acinar cells, ramping up enzyme production and pancreatic inflammation to accelerate tumorigenesis (Zhang et al. 2023). Meanwhile, islet production of CCK can act locally on acinar cells to facilitate ADM (Chung et al. 2020); this effect could be reversed by caloric restriction, but not anti-inflammatory treatment, prior to tumor development. These studies indicate that correcting endocrine function may ameliorate obesity-associated tumorigenesis, perhaps independent of inflammation in some cases, though the window for intervention may be limited to early disease. It is important to note that metabolic syndrome is often associated with microbial dysbiosis; given the emerging association between the microbiome and PDAC, the mechanistic contribution of microbes to inflammation and cancer development will be an important avenue for future exploration (Eibl & Rozengurt 2021, Ruiz et al. 2023).

While inflammation encourages early tumor development, tumor progression in turn drives an associated unresolved inflammatory reaction as cancer cells continuously reshape the tumor microenvironment (TME) (Stone & Beatty 2019). Pancreatic tumors, driven at least in part by *Kras* signaling (Kemp et al. 2023, Mahadevan et al. 2023), stimulate an influx of macrophages, myeloid cells, neutrophils, and regulatory T cells (Tregs) that foster a protumorigenic immunosuppressive environment that hinders response to immunotherapy (Stone & Beatty 2019). Important executors of the immune response including CD8 T cells, natural killer cells, and antigen-presenting dendritic cells (DCs) exhibit signs of exhaustion and dysfunction within the tumor (Yousuf et al. 2023). Comprehensive spatial and single-cell analyses of PDAC tumors affirm that elevated infiltration of CD8 T cells relative to macrophages is associated with better survival in patients (Liudahl et al. 2021, Yousuf et al. 2023); thus, strategies to ameliorate the immunosuppressive landscape could benefit patients and possibly permit response to immunotherapy. To this end, a number of clinical strategies have been employed to reduce the infiltration of immunosuppressive M2-like tumor-associated macrophages (TAMs) or redirect their functional state (DeNardo & Ruffell 2019). Most notably, agonists of the cell surface receptor CD40 have shown some activity in PDAC, through both macrophages and DCs (Bear et al. 2020, Stone & Beatty 2019). Boosting DC infiltration can also improve antigen-specific tumor control in GEMMs (Hegde et al. 2020), suggesting that sensitization to immunotherapy may require combination strategies to improve both DC and CD8 T cell infiltration and their tumoral function, likely paired with reprogramming of immunosuppressive macrophages. The challenges of overcoming immunosuppression have been reviewed extensively (Bear et al. 2020), but the ambitious pursuit of these strategies clinically may eventually allow PDAC patients to benefit from immunotherapy.

DESMOPLASTIC STROMA

Closely tied to inflammation, the desmoplastic stroma is another important feature of PDAC. Pancreatic tumors are characterized by a dense fibrotic stroma that can compose over 90% of the tumor volume, made up of a stiff extracellular matrix (ECM) as well as infiltrating immune cells and fibroblasts. The rigid ECM, produced by cancer-associated fibroblasts (CAFs), deforms vasculature and impairs drug delivery, while stromal signals support drug resistance and metastasis. For these reasons, the stroma was largely thought to have a tumor-supportive function, and ablation of stromal CAFs was considered a therapeutic goal; however, the tumor–stroma relationship

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has proven to be more complex than initially anticipated (Caligiuri & Tuveson 2023, Hosein et al. 2020). We have proposed that CAFs can be broken down into three major subtypes with independent functions and impact on tumor biology: myofibroblastic CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs) (Caligiuri & Tuveson 2023, Elyada et al. 2019, Öhlund et al. 2017). myCAFs are enriched for the expression of activated smooth muscle actin (αSMA) and collagens, and they are located proximal to tumor cells where they remodel the ECM. iCAFs are located further from tumor cells, engaging in immune cell recruitment via paracrine cytokine signals such as IL-6 (Caligiuri & Tuveson 2023, Elyada et al. 2019, Öhlund et al. 2017). apCAFs express major histocompatibility complex II genes and similarly modulate the immune TME, specifically driving the induction of immune-suppressive Tregs (Huang et al. 2022).

Although the functional relevance of CAF subtypes is only beginning to emerge, prior work aimed at ablating CAFs via Hedgehog (Hh) inhibition provided initial insight into the complexity of targeting the stroma. Hh signaling is enriched within αSMA+ myCAFs, and promising preclinical results showed that Hh inhibitors depleted αSMA+ CAFs and reduced fibrosis, improving drug perfusion and chemosensitivity in mice (Olive et al. 2009). However, Hh inhibition or genetic αSMA+ CAF depletion worsened metastasis, cachexia, and overall survival in GEMMs in line with the clinical failure of Hh inhibitors (Hosein et al. 2020, Özdemir et al. 2014, Rhim et al. 2014). Subsequent work showed that αSMA+ myCAF depletion caused concurrent iCAF expansion, driving immune suppression in mice (Steele et al. 2021). Compensatory iCAF expansion may be explained by changes in TGFβ signaling. A key driver of the myCAF state, TGFβ antagonizes IL-1-mediated iCAF activation (Biffi et al. 2019); thus, CAF TGFβ suppression by Hh inhibitors may antagonize myCAF in support of iCAF fate. Together, these studies suggest that effectual stromal therapies will need to address both desmoplastic and immunosuppressive CAF functions. Although iCAF-specific Cre drivers have not yet been designed, broad genetic ablation of CAFs using fibroblast activation protein, FAP+, alleviated immunosuppression, sensitizing PDAC tumors to immunotherapy (Feig et al. 2013, Kraman et al. 2010). The iCAF-enriched cytokine CXCL12 was found to drive T cell exclusion, nominating inhibitors of CXCL12 or its cognate receptor, CXCR4, as putative targets for disrupting iCAF function and sensitizing to immunotherapy (Feig et al. 2013). As key regulators of the iCAF state, IL-1 and its effectors LIF, IL-6, and JAK/STAT may also represent important targets for iCAF suppression (Biffi et al. 2019). In the future, combining iCAF-targeted therapies with inhibitors aimed to interrupt protumorigenic myCAF functions may be the path forward for remodeling the PDAC stroma to achieve clinical benefit. apCAFs are proposed to arise from mesothelial cells, and treatment with a Mesothelin (MSLN) antibody has been shown to reduce apCAFs, Tregs, and tumor burden in vivo (Huang et al. 2022). MSLN is highly expressed by PDAC cells, so the apCAF-specific nature of these effects is unclear; nonetheless, they provide some evidence that cotargeting of apCAFs and tumor cells with this approach could have antitumor efficacy.

An alternative paradigm for targeting the stroma is to identify subtype-agnostic protumorigenic CAF functions to disrupt therapeutically. One emergent common protumorigenic CAF function is the production of metabolites that support cancer cell survival in the nutrient-poor TME (Auciello et al. 2019, Dalin et al. 2019, Dey et al. 2021, Encarnación-Rosado & Kimmelman 2021, Murthy et al. 2024, Sousa et al. 2016). Subtype-independent production of acetate by CAFs has been shown to orchestrate histone acetylation and epigenetic reprogramming in pancreatic cancer cells, promoting their survival at low pH (Murthy et al. 2024). Pancreatic stellate cells (PSCs), a known origin of PDAC CAFs, also support cancer cell proliferation in nutrient-limited conditions through alanine production (Sousa et al. 2016). Conversely, CAF functions such as collagen production can be metabolically constrained (Schwörer et al. 2021). As this field continues

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to grow, metabolic CAF–tumor cross talk may reveal interesting new paths for intervention. Another subtype-agnostic paradigm for targeting the stroma is stromal reprogramming of activated CAFs to a quiescent state. To this end, vitamin D receptor (VDR) has been implicated as a master regulator of PSC activation and a putative target for CAF reprogramming. VDR activation reduced fibrosis and improved chemosensitivity in mice (Sherman et al. 2014), leading to clinical investigation of this strategy for the treatment of PDAC (Hosein et al. 2020). Direct targeting of CAF-produced ECM may be another approach to tune the physical qualities of the stroma independent of CAF biology; however, clinical targeting of ECM proteins has so far been unsuccessful (Hosein et al. 2020). Like CAF targeting, ECM modulation can have complex and contradictory effects on tumor biology. For example, recent preclinical studies targeting lysyl oxidase enzymes reduced collagen cross-linking and fibrosis but yielded opposing outcomes. Inhibition of LOXL2 via monoclonal antibody treatment promoted tumor growth in orthotopic models (Jiang et al. 2020), while a novel pan-lysyl oxidase inhibitor improved survival, chemosensitivity, and metastatic burden in an autochthonous PDAC model (Chitty et al. 2023). Therefore, we still have work to do to identify stromal therapeutic targets with clear-cut benefits for tumor inhibition.

EARLY METASTASIS

Another critical contributor to PDAC mortality and an important hallmark of the disease is early metastasis. Evidence from GEMMs has shown that metastatic spread can occur as early as the PanIN stage in disease progression, indicating dissemination that surprisingly preceded the histological emergence of frank cancer (Rhim et al. 2012). Supporting this model of early dissemination, a majority of patients who undergo tumor resection will have recurrence within 2 years, indicating that micrometastatic spread occurred in the case of apparently local disease (Groot et al. 2018). Identifying the cause of aggressive metastasis is therefore critical to tackle PDAC clinically. Interestingly, evolutionary analyses of matched primary and metastatic lesions in patients revealed that metastasis is not largely driven by specific mutations (Hayashi et al. 2021, Makohon-Moore et al. 2017). Instead, metastases are characterized by large-scale epigenetic reprogramming (McDonald et al. 2017, Roe et al. 2017), implicating nongenetic tumor heterogeneity as an important driver of the phenotypic changes required for tumor cell invasion, dissemination, and metastatic colonization. The phenotypic shift implicated in this metastatic cascade is called epithelial-to-mesenchymal transition (EMT); EMT involves a loss of epithelial gene expression and a morphological shift to a mesenchymal cell state associated with loss of cellular polarity and enhanced invasive ability (Dongre & Weinberg 2018).

Through the study of EMT in cancer, it has become increasingly clear that tumor cells exist on a spectrum between epithelial and mesenchymal phenotypic poles. Hybrid or partial EMT states have been described and have been implicated in collective migration, organotropism, and clonal metastatic propagation (Aiello et al. 2018, Dongre & Weinberg 2018, Reichert et al. 2018, Simeonov et al. 2021). In human tumors, epithelial and mesenchymal states largely correspond to classical and basal transcriptional PDAC subtypes, respectively (Bailey et al. 2016, Collisson et al. 2011, Moffitt et al. 2015); however, heterogeneity among human tumors is more complex. The basal subtype overlaps with quasi-mesenchymal and squamous subtype classifications identified by other groups, which, although somewhat distinct, share a poorer prognosis and enrichment for EMT features relative to the classical subtype (Di Chiaro et al. 2024, Hayashi et al. 2020, Rashid et al. 2020). Interestingly, recent work in GEMMs indicates that the basal and classical subtypes correspond to ductal and acinar-derived tumors, respectively, suggesting a possible role for cellular origin in determining subtype identity (Flowers et al. 2021). Adding further complexity, an undifferentiated and therapy-enriched subtype characterized by a neural progenitor signature has

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also been identified in human tumors (Di Chiaro et al. 2024, Hwang et al. 2022). Although the relationship between subtypes remains unclear, basal/mesenchymal and classical/epithelial features can coexist within the same cell (Chan-Seng-Yue et al. 2020, Raghavan et al. 2021, Williams et al. 2023), implying some conversion from one differentiation state to another. Supporting cell state transition in disease progression, we used pseudotime analysis of single-cell RNA sequencing of mouse tumors to show that precancerous epithelial^{High} cells progress through a hybrid state toward a mesenchymal fate (Tonelli et al. 2024). Epithelial^{High} cells were enriched for the expression of genes implicated in mucus secretion, including the transcription factor *Spdef*. *Spdef* deletion impaired epithelial/classical tumor growth in vivo while upregulating basal/EMT programs, demonstrating that although *Spdef* may represent a classical subtype-specific dependency, its targeting would likely lead to basal subtype tumor outgrowth (Tonelli et al. 2024). Genetic ablation of classical subtype regulatory factors including *Gata6* has yielded similar results, driving basal/mesenchymal tumor differentiation and higher metastatic burden (Kloesch et al. 2022, Lan et al. 2022). These results indicate that targeting of basal/mesenchymal cell fate will ultimately be required to effectively treat PDAC and prevent metastasis. Several key regulators of basal/mesenchymal cell fate have been identified (Adams et al. 2019, Andricovich et al. 2018, Brunton et al. 2020, Du et al. 2021, Tu et al. 2021), including the tyrosine kinase *Axl*. AXL is enriched in mesenchymal tumor cells, and its global deletion or inhibition in mice promoted epithelial tumor differentiation and improved survival, chemosensitivity, and T cell infiltration while reducing metastasis (Du et al. 2021, Zhang et al. 2022).

Although stepwise progression from epithelial to mesenchymal fate is a logical paradigm for understanding PDAC progression, hybrid cancer cells may instead exhibit bidirectional plasticity. In a recent single-cell analysis of mouse tumors, a transitional population of basal tumor cells was identified; these cells exhibited bivalent chromatin accessibility at epithelial and mesenchymal genes, poised for bipotent plasticity. Indeed, when the basal marker *Lgr5* was used to lineage trace tumor cells in vivo, *Lgr5*+ cells gave rise to both classical and mesenchymal progeny (Pitter et al. 2022). These results suggest a model in which plastic transitional cells fuel tumor heterogeneity, drawing parallels to the cancer stem cell (CSC) model in which stemlike cancer cells enriched for developmental programs preferentially contribute to tumor heterogeneity, therapy resistance, and metastasis. This model suggests that specific targeting of plastic cancer cells or CSCs may be required to disrupt tumor progression and metastasis (Batlle & Clevers 2017). A model of bipotent plasticity also begs the question, What extrinsic factors influence differentiation trajectories? Spatial profiling has demonstrated that regional TME heterogeneity is associated with the PDAC differentiation state in vivo (Di Chiaro et al. 2024, Grünwald et al. 2021). This is supported by our own work showing that the differentiation state of isogenic PDOs can be determined by TME context in intraductal versus parenchymal transplant models (Miyabayashi et al. 2020). In organoid models, TGFβ and interferon-γ have been shown to push tumor cells toward a basal or intermediate cell state, respectively, in vitro, further implying direct TME regulation of subtype identity (Raghavan et al. 2021). These studies open up many new questions for envisioning therapy. Which cell states should be targeted therapeutically to impede metastasis? Further, if the TME regulates malignant cell fates, will TME modulation be necessary to subvert the metastatic cascade?

KRAS SIGNALING

Occurring in over 90% of PDAC, mutant *KRAS* is a requisite driver for pancreatic cancer. KRAS is a small GTPase that is targeted for single–amino acid substitutions that lock the protein in the GTP-bound conformation and drive constitutive activation of effectors such as the PI3K/AKT

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and RAF/MEK/ERK pathways (Singhal et al. 2024). In pancreatic cancer, studies using the inducible iKras GEMM to extinguish *Kras*^{MUT} activity have provided preclinical evidence that loss of mutant KRAS activity is sufficient to drive tumor regression (Collins et al. 2012a,b; Ying et al. 2012). KRAS amplification has also been associated with invasive, basal PDAC (Chan-Seng-Yue et al. 2020, Miyabayashi et al. 2020), further affirming the rationale for therapeutic targeting of Ras. After years of KRAS being considered structurally undruggable, recent advances have finally culminated in the design of KRAS inhibitors. The first of these to reach the clinic were inhibitors targeting the *KRAS*^{G12C} mutation, which is rare in PDAC but common in lung cancer. Small molecules have since emerged to target the more PDAC-prevalent KRAS^{G12D} mutation, as well as pan-Ras activity (Singhal et al. 2024). Preclinical studies have established the efficacy of these strategies in PDAC; both the KRAS^{G12D}-specific inhibitor MRTX1133 (Kemp et al. 2023, Mahadevan et al. 2023) and the pan-Ras inhibitor RMC-7977 (Wasko et al. 2024) demonstrated potent antitumor activity in GEMMs. Nonetheless, mice eventually succumbed to disease, mirroring the results of KRAS^{G12C} inhibitor clinical trials where overall response rates were modest and patients exhibited acquired and intrinsic resistance (Singhal et al. 2024). Although clinical trials are ongoing to evaluate KRAS^{G12D} and pan-Ras inhibitors, outcomes are likely to be similar. Therefore, while KRAS inhibitors have the potential to transform PDAC treatment, future efforts will need to focus on identifying actionable dependencies in KRAS-independent relapsing tumors.

While clinical assessment of KRAS inhibitors in PDAC is underway, studies in iKras mice have provided some insight into predicted mechanisms of resistance to *Kras*^{G12D} inhibition. Tumors emerging after *Kras*^{G12D} ablation were poorly differentiated and relied on YAP1 (Kapoor et al. 2014) and MYC (Genovese et al. 2017) signaling, as well as upregulation of metabolic pathways including oxidative phosphorylation (Viale et al. 2014) and micropinocytosis (Hou et al. 2021). Supporting MYC as a putative drug resistance mechanism, a CRISPR screen conducted in combination with MRTX1133 found that disruption of MYC, SHP2, EGFR, and PI3K signaling synergized with KRAS^{G12D} inhibition (Hallin et al. 2022). Interestingly, studies in GEMMs have shown that TME signals can also support tumor bypass of *Kras*^{G12D} dependence. For example, ERBB2/ERRB3 activation by CAF-produced NRG1 supported tumor growth after *Kras*^{MUT} was extinguished (Han et al. 2023). *Kras*^{G12D} ablation also drove an influx of TAMs; TAM-produced TGFβ in turn supported the growth of *Kras*^{G12D}-independent tumors (Hou et al. 2020). Preclinical studies using MRTX1133 similarly found that *Kras*^{G12D} inhibition remodeled the immune microenvironment (Kemp et al. 2023, Mahadevan et al. 2023) but promoted CD8 T cell infiltration, indicating a potential synergy between *Kras*^{G12D} inhibition and immunotherapy that merits further exploration. Together, these indicate a broad range of pathways that may drive clinical resistance to KRAS^{G12D} inhibitors and a vast array of opportunities for combination therapy. One further consideration for the utility of mutant-specific targeting of KRAS is the potential for wild-type Ras activity to drive adaptive resistance. To identify potential direct regulators of wild-type and mutant KRAS activity, we used a proximity ligation approach and found that the kinase RSK1 specifically interacted with membrane-bound KRAS^{MUT}, dependent on NF1 and SPRED2. When *Kras*^{MUT} was ablated, loss of membrane RSK1 led to derepression of wild-type Ras signaling, which we hypothesize could act as a putative mediator of resistance to Kras^{G12D} inhibition (Cheng et al. 2021). To this end, it will be interesting to see if pan-Ras inhibitors provide clinical benefit over mutant-specific inhibitors by preventing bypass signaling from wild-type Ras. Although this approach may cause broader side effects, it may also restrict the resistance mechanisms available to tumor cells. In preclinical studies, pancreatic tumors that regrew after treatment with RMC-7977 exhibited amplifications in MYC and sensitivity to YAP inhibition (Wasko et al. 2024), suggesting that pan-Ras inhibition may select for specific alternative signaling pathways in lieu of bypass

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activation of RAS/MAPK signaling as has been observed in response to $KRAS^{G12C}$ inhibitors (Singhal et al. 2024).

METABOLISM

Dysregulated metabolism has long been recognized as an important feature of cancer (Pavlova et al. 2022), and PDAC is no exception. Mutant *Kras* drives extensive reprogramming of core metabolic pathways including glucose and glutamine utilization, mitochondrial respiration, and nutrient scavenging to fuel proliferation and manage oxidative stress (Commisso et al. 2013, Denicola et al. 2011, Encarnación-Rosado & Kimmelman 2021, Kamphorst et al. 2015, Son et al. 2013, Viale et al. 2014, Yang et al. 2011, Ying et al. 2012). To interrogate metabolic pathways active in vivo, recent studies have used CRISPR screens to pinpoint functional metabolic dependencies in mice (Biancur et al. 2021, Zhu et al. 2021). These studies found striking concordance between metabolic dependencies in vitro and in vivo, affirming the use of in vitro systems for metabolic profiling, while also revealing a unique dependency on heme biosynthesis in vivo (Biancur et al. 2021, Zhu et al. 2021). Dependence on heme synthesis was masked in vitro by compensatory heme production in neighboring cells. The unmasking of this requirement in vivo highlights the divergence in metabolic cross talk, perhaps complicated by the stroma, in vivo. However, in general, the ability of metabolically diverse tumor cells to complement each other represents a challenge for therapeutic targeting of cancer metabolism. As discussed, tumor–stroma metabolic cross talk is increasingly recognized as contributing to tumor growth; similarly, we can speculate as to whether complementary relationships exist among tumor cell types (Dey et al. 2021). Metabolic heterogeneity within tumors is only beginning to be explored, and its implications are not entirely clear. Basal and classical PDAC subtypes, for example, have been associated with glycolytic or lipogenic metabolic profiles, respectively, and demonstrate subtype-specific sensitivity to the inhibition of these pathways (Brunton et al. 2020, Daemen et al. 2015). It is possible that understanding these phenotype-specific metabolic dependencies could guide the clinical application of metabolic inhibitors. Conversely, metabolic heterogeneity may bolster the tumor's capacity for metabolic adaptation, compounding the effects of compensatory rewiring to make clinical targeting of metabolism even more challenging (Biancur et al. 2017). Despite these challenges, inhibitors targeting nutrient scavenging via autophagy have shown some activity when combined with MEK/ERK inhibitors and remain under clinical investigation (Dey et al. 2021, Encarnación-Rosado & Kimmelman 2021). Interestingly, this is in line with studies demonstrating that cancer cells surviving $Kras^{MUT}$ ablation are uniquely dependent on autophagy (Viale et al. 2014). As KRAS inhibitors reach the clinic, they may impose a bottleneck on metabolic plasticity; thus, arising metabolic dependencies may become effective targets in drug-resistant tumors.

Metabolic context can also shape tumor heterogeneity by imposing selection pressures on tumor cells. This can be seen in early tumorigenesis, where low oxygen or glucose conditions can select for the emergence of specific oncogenic mutations (Yun et al. 2009). Tumor metabolic conditions can also promote EMT, exerting selection pressure that favors metastasis. Glutamine restriction, for example, can drive EMT and ERK activation; activation of these programs confers a survival benefit on glutamine-starved cells (Recouvreux et al. 2020) that could shape phenotypic tumor evolution in the nutrient-poor TME. Metabolic by-products also regulate cell fate by directly modifying protein function. Isoprenoids, for example, are a by-product of the mevalonate pathway required for Ras prenylation, membrane localization, and activity. In our own work, we found that metastatic organoids uniquely depend on the upregulation of sterol *O*-acyltransferase 1 (SOAT1) to prevent negative feedback inhibition of the mevalonate pathway, enabling isoprenoid production and Ras prenylation (Oni et al. 2020b). Another important example of direct

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metabolic control of cell signaling is the metabolism of glucose to acetyl–coenzyme A (CoA). Glucose-derived citrate can be used to produce acetyl-CoA via ATP-citrate lyase (ACLY). In turn, acetyl-CoA is used to acetylate histones, a protein modification that modulates chromatin accessibility and function. In PDAC, $Kras^{MUT}$ increases the flux of glucose into acetyl-CoA, driving ADM, tumorigenesis, and associated increases in global histone acetylation (Carrer et al. 2019). Distant metastases have also been shown to upregulate glucose avidity, fueling global acetylation and epigenetic remodeling at large chromatin regions that encode tumorigenic programs including EMT (Bechard et al. 2020, McDonald et al. 2017). This is a unique illustration of how metabolic selection pressure for enhanced glucose uptake can in turn reprogram cell fate and promote metastasis, dependent on direct protein modification by a metabolic by-product. Although the direct relationship between metabolism and epigenetic regulation has become more apparent (Morris et al. 2019), there is likely much we do not yet understand regarding the role of metabolites as signaling molecules. Within the heterogenous pancreatic TME, spatially irregular nutrient availability could exert broad and unanticipated effects on cell fate and tumor evolution.

RAPID DECONDITIONING

The final hallmark of PDAC that we discuss is rapid deconditioning, or the rapid physiological deterioration that often accompanies a pancreatic cancer diagnosis. Late diagnosis means that PDAC patients often present with advanced disease accompanied by physiological decline due to pancreatic exocrine insufficiency and malnutrition, weight loss, and a fat and muscle wasting syndrome called cachexia (Grossberg et al. 2020). Cachexia in particular is extremely prevalent in PDAC, and it is associated with worse outcomes in the context of both therapy and surgical resection (Babic et al. 2019, Bachmann et al. 2008, Kays et al. 2018). Development of effective strategies to prevent or treat cachexia could have important implications for quality of life, as well as tolerance and response to therapy. Cachexia is a complex multifactorial syndrome that represents a convergence of cancer-associated inflammation and metabolic dysfunction (Ferrer et al. 2023). Tumors and the associated TME produce cytokines that promote adipose and muscle catabolism, mobilizing nutrients that are exploited by tumors. Tumor-associated signals also drive adipose browning, which can worsen whole-body energy balance. Moreover, inflammatory mediators signal directly to the central nervous system, which suppresses appetite and further exacerbates tissue catabolism. Clinical trials are ongoing to test drugs that stimulate appetite or block cachexia-associated inflammatory signaling; however, no specific therapies have been approved to date (Ferrer et al. 2023). In part, clinical trials to treat cachexia remain challenging as they typically involve the enrollment of patients with >5% weight loss, representing late-stage progression of cachexia. In reality, tissue wasting may precede diagnosis by up to 2 years (Babic et al. 2023), suggesting that strategies to manage cachexia earlier are likely necessary.

In lieu of effective interventions for cachexia, rapid deconditioning constrains the time frame in which patients can tolerate therapy. This warrants the development of precision medicine approaches that empower clinicians to choose therapies wisely. To achieve this, some efforts have focused on matching therapy to actionable genetic alterations. For example, patients with *BRCA1/2* mutations can benefit from DNA repair–targeting PARP inhibitors (Golan et al. 2019), and the rare population of patients exhibiting mismatch repair deficiency may benefit from immunotherapy (Marabelle et al. 2020). A review of patients referred for genetic profiling showed that of the ~25% of patients with actionable genetic alterations, those that received matched therapy saw a survival benefit (Pishvaian et al. 2020). Nonetheless, the many patients without actionable genetic mutations will require personalized therapy based on nongenetic tumor features. The correlation of transcriptional PDAC subtype with chemosensitivity (Rashid et al. 2020) suggests that RNA sequencing (RNA-seq) may be useful in directing personalized

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medicine. Indeed, recent work has leveraged RNA-seq to develop bioinformatic tests to predict actionable signaling axes that may be targeted to disrupt patient-specific transcriptional states or their master regulators (Mundi et al. 2023). In an effort to bypass a reliance on sequencing data, we have instead leveraged PDOs to develop a rapid drug screening platform to directly predict patient-specific therapy response within a clinically relevant time window. In a preclinical study, we showed that rapid (~15 days) organoid establishment and screening was possible and that drug sensitivity in organoids was predictive of patient response (Demyan et al. 2022, Tiriac et al. 2018). We are now exploring the feasibility of this approach in the PASS-01 clinical trial (Knox et al. 2022). Another innovative strategy being pursued in the treatment of surgically resected patients is a personalized messenger RNA (mRNA) vaccine. Custom designed based on patient-specific neoantigens, mRNA vaccines were rapidly produced and administered after resection, where they activated an immune response and delayed recurrence in ~50% of patients in a small trial (Rojas et al. 2023). Though preliminary, this approach has the potential to improve survival in surgery-eligible patients. These results also suggest that personalized immunotherapy in PDAC may be possible, especially if we can identify patients capable of activating an immune response; this may become increasingly relevant as KRAS inhibitors enter the clinic and potentially alleviate immunosuppression (Kemp et al. 2023, Mahadevan et al. 2023).

CONCLUSIONS AND OPEN QUESTIONS

While each of the disease hallmarks outlined here represents an individual challenge that must be addressed to work toward a cure for pancreatic cancer, we hope that we have highlighted the many junctures at which these disease features are closely interconnected. While addressing diagnostic deficiencies will widen the net to capture a larger number of patients with early-stage disease, the aggressive metastatic spread underlying tumor recurrence still necessitates the development of strategies to block malignant disease progression or prevent tumorigenesis altogether. As our understanding of tumors progression has evolved, it has become clear that heterogeneity among tumor cells and the TME is a central problem we will need to address to effectively tackle this disease. Heterogeneity and plasticity among tumor cells are a source of resistance to therapy and are closely tied to TME signaling and metabolic context in the tumor. In turn, diverse tumor phenotypes reciprocally shape the TME landscape, whose heterogeneity similarly drives poor prognosis. Deeper bioinformatic exploration of spatial and single-cell tumor analyses enables the systematic dissection of relevant axes of tumor–stroma communication, and future biological exploration of these relationships may change the way we think about blocking tumor progression. Perhaps we will be able to identify actionable signaling nodes that can destabilize tumor–TME networks by concomitantly regulating malignant cell fate and immunosuppression. Furthermore, as metabolomic techniques continue to improve, we will begin to incorporate this information into our understanding of tumor–TME networks and their regulation. As a final note, the likely clinical adoption of KRAS inhibitors in the near future will surely represent a shift in the pancreatic cancer landscape. Although we do not know the extent to which these inhibitors will influence patient outcomes, the ability to disrupt this central oncogene will surely impact the nature and trajectory of this disease. This represents an exciting time for PDAC research, as we have the opportunity to begin the serious exploration of how to approach this critical hallmark in patients for the first time.

DISCLOSURE STATEMENT

L.P.F. has no disclosures that might be perceived as affecting the objectivity of this review. D.A.T. is a member of the Scientific Advisory Board and receives stock options from Leap Therapeutics,

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