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REVIEW OPEN ACCESS

Exploring the Therapeutic Opportunities of the Tumour Microenvironment in Treating Pancreatic Ductal Adenocarcinoma: A Literature Review

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Abstract

Introduction: Pancreatic ductal adenocarcinoma (PDA) is an invasive cancer of the exocrine pancreas with a 5-year survival rate (<8%), highlighting the need for new therapies to increase patient survivability and remission rates. Current treatment options with chemotherapeutics have yielded minimal success, warranting further research into targeting alternative pathways in tumour progression. The complex tumour microenvironment (TME) of PDA contributes significantly to tumorigenesis and may contain promising novel targets. The therapeutic potential of some known TME elements will be explored, namely hypoxia, MMPs, and TGF-β. These options each have their merits and differences, which are crucial to evaluate and assess the trajectory of PDA research in the future.

Methods: A literature review was performed to summarize all available research on the different current therapeutic options and TME components that can be utilized for PDA treatment. The terms "hypoxia," "MMPs," and "TGF- β" were used as keywords to search databases including Medline, Embase, and CINAHL. These were searched in combination with terms relevant to PDA and TME. Studies that were peer-reviewed and written in English were taken into consideration, with a focus on those that were published between 2017 and 2022.

Results: Each TME element of hypoxia, MMPs, and TGF-β have specific distinctive targets of HIF-1α, TIMP-1, and SMAD-independent pathways, respectively. These present varying mechanisms of action which differ in their efficacies and limitations. Several of these therapies are currently undergoing clinical trials to better understand the role of each inhibitor.

Discussion: This literature review provides insight into the current and future treatments for PDA. Exploiting the TME to develop therapeutic interventions presents a promising strategy to inhibit disease progression, yet research done in PDA is still preliminary due to the disease complexity, but it is moving towards a clinical settings.

Conclusion: Accumulating evidence has suggested that several opportunities for targeted therapy in the PDA TME are very promising and not yet thoroughly investigated. This review aids in accessibility by summarizing important information regarding PDA and the necessary further research into targeting the TME to develop a novel therapeutic treatment.

Keywords: pancreatic ductal adenocarcinoma; tumour microenvironment; metastasis; hypoxia; matrix metalloproteinases; transforming growth factor-β

Introduction

Despite the substantial progress in our understanding of etiology and cancer progression, pancreatic ductal adenocarcinoma (PDA) is the fourth most prevalent cause of cancer-related deaths among people globally, and its incidence continues to rise [1]. It is an invasive malignant cancer deriving from ductal epithelial cells of the exocrine pancreas with a 5-year survival rate below 8% [2]. Its dismal prognosis is partly due to late diagnoses as approximately only 15% of PDA patients are eligible for surgical resection at diagnosis, which is one of the limited remedial options when combined with chemotherapy [3]. Moreover, while all cancers have many of the same characteristics, PDA produces large tumours that disseminate and relapse, negatively impacting the patient and evading therapies that are effective in other cancers [4]. Additionally, detecting PDA is extremely difficult with traditional visualization modalities due to limited sensitivity. Therefore, the lack of detection and operability in PDA treatment creates an urgent need in preventing PDA by reducing risk factors and diagnosing earlier.

Although difficult to treat, some treatment options are available for advanced PDA. While surgery is the ideal treatment option, virtually all patients are asymptomatic in the early stages of PDA, with 90% of patients obtaining advanced stages diagnoses [4-6]. Here, metastatic tumours complicate surgical procedures. In these cases, chemotherapeutic regimens are implemented to reduce tumour progression. Gemcitabine (Gem) and modified FOLFIRINOX (mFFX) are the current gold-standard treatment for all stages of PDA,

with other neoadjuvant currently under investigation [7,8]. However, both acquired chemoresistance and surgical invasiveness have called for other treatment options.

In recent years, research on targeted-, microbial-, and immune-therapy has become increasingly prevalent in treating various forms of cancers [9]. While targeted therapy, such as vascular endothelial growth factor (VEGF)-directed antibodies have shown success in other cancer types, a plethora of adverse effects including induced toxicity and tumour recurrence were observed in PDA making it unfeasible for treatment [10-12]. Microbial therapy and immunotherapy, on the other hand, have focused on the tumour microenvironment (TME) of PDA as a potential therapeutic target [13,14]. Mei et al. discovered that the TME of PDA patients exhibited lower bacterial diversity when compared to patients with pancreatic cysts and healthy controls [15]. Moreover, immune checkpoint blockade (ICB) therapy is another FDA-approved method to treat the immunosuppressive TME of PDA that promotes growth and invasion [16,17]. These strategies present interesting approaches by targeting the TME and warrant further investigation to develop an effective therapeutic regimen.

With the influential role of the TME in PDA progression, research has now moved towards determining the potential of targeting components of the TME; these include hypoxia, matrix metalloproteinases (MMP), and transforming growth factor-β (TGF-β). Extreme hypoxic regions are prevalent in PDA, primarily characterized by inadequate homeostasis due to insufficient oxygen levels [18]. PDA stroma has been implicated in acting as a physical barrier to chemotherapy and the diffusion of oxygen, leading to cell resistance and aggressive malignancy by surviving cells [19]. Thus, targeting this region using anti-hypoxic therapy or hypoxia-activated prodrugs (HAPs) to promote oxygen association could be a non-invasive strategy to prevent PDA and resistance. Moreover, PDA proteases, proteolytic enzymes involved in degradation, play an important role in tumour-stromal cell communication, including MMPs. Abnormal MMP expression in the TME has been implicated in disrupting extracellular matrix (ECM) homeostasis, consequently driving PDA progression [20,21]. By designing MMP inhibitors (MMPI), the tumour mass can be decreased and localized to increase resectability [22]. Lastly, TGF-β is widely considered a strong candidate for novel therapeutics, with mutations occurring in 50 to 60% of recorded cases [23,24]. Targeting TGF-β in ligand-receptor binding and in intracellular signal transduction to disrupt signalling, may inhibit PDA progression [25].

In this review, recent insights into TME components and their potential for novel therapeutic opportunities will be discussed. Current strategies leveraging the known TME of PDA will be highlighted; including targeting and manipulating hypoxia, MMPs, and TGF-β present in the harsh environment. Further, the ramifications and available data will be explored to determine possible implications and the future viability of these techniques.

Methods

An extensive literature search was conducted using several databases: MEDLINE via PubMed (1996 to 2022), Embase (2000 to 2022), and CINAHL (2008 to 2022) on July 27, 2022. An emphasis on published papers between 2017 to 2022 was made. Clinical trial databases, research articles, and the reference lists of retrieved papers were examined for randomized controlled studies, which included TME components. Only papers authored in English and published in peer-reviewed journals were taken into consideration. Keywords were employed for the search of primary topics (TME and PDA) combined with terms related to TME function, structure, and possible treatment outcomes (using Boolean operators "OR/AND/NOT") to gain a comprehensive understanding. An emphasis was made on research published between 2017 and 2022 to focus specifically on the most recent data published.

Results

The TME has a significant impact on the growth and development of PDA. PDA development can be triggered by the acquisition of oncogenic KRAS mutations and tumour suppressor gene abnormalities. However, PDA development involves more complex interactions, including those within the TME such as the cancer-associated fibroblasts (CAFs) that induce hypoxia, the enzymatic breakdown of the ECM causes tumour invasion via MMPs, and TGF-β dysregulation promoting carcinogenesis [4,26,27]. Focusing on these components in the TME has the potential to provide strong targets for novel therapeutic interventions to revolutionize PDA management.

Targeting the Hypoxic TME Regions

Hypoxia describes an environment with oxygen levels below normal which impedes cell homeostasis. Hypoxic pockets in PDA are associated with tumour growth and a poor prognosis [28]. PDA is extremely hypoxic, with a median oxygen level of less than 0.7% compared to neighbouring tissue at approximately 1.2–12.3% [28,29]. This may be explained by the Warburg effect, wherein glycolysis is used in place of oxidative phosphorylation, hence lactate secretion and the conversion of glutamine to glucose aids in tumour cell survival in low oxygen conditions [28,30,31]. Although these pathways in PDA contribute to cancer aggressiveness, they also indicate a gap between normal and PDA metabolism and tumour growth that may be exploited for novel target identification and intervention.

In response to the hypoxic TME, hypoxia-inducible factors (HIFs) are activated to upregulate genes for cell survival in low oxygen concentrations [32,33]. As HIF proteins are the primary controllers of oxygen homeostasis in hypoxia, targeting HIFs for cancer therapy is a promising

approach. Several strategies that could be exploited include: (1) modulating HAPs and (2) targeting HIFs to alter downstream signalling pathways.

The first strategy involves utilizing HAPs to modulate HIFs. Currently, no HAPs are approved by the FDA, although several have shown therapeutic potential. For example, evofosfamide (TH-302) is a HAP specifically activated in PDA-like severe hypoxic TME settings [34-36]. Here, the radical engages in redox cycling with a prolonged half-life, resulting in fragmentation and the production of the active drug in hypoxic cells. In a series of xenograft models, TH-302 has demonstrated targeted degradation of hypoxia cells by selectively binding to DNA and eliminating malignant cells [37-39]. Additionally, preclinical research by Sun et al. showed that activating the moiety (Br-IPM) of TH-302 induced DNA damage and selectively targeted hypoxic tumour tissue of PDA for degradation [40,41]. Further investigation into TH-302 for use in PDA is necessary to leverage its use as an alternative anticancer therapy.

Another method to target the hypoxic TME is to inhibit specific HIF pathways in PDA. HIF-1α is a heterodimer protein overexpressed under hypoxic conditions in PDA and associated with a poor prognosis [42]. HIF-1α also facilitates the proliferation of cancer cells by promoting neovascularization and dissemination. Research by Hao et al, revealed that HIF-1 binds to the promoter of actin-binding proteins promoting metastasis [7]. Furthermore, NF-κB transcription factors were reported as targets of HIF-1α involved in controlling tumour growth and enabling chemoresistance [43,44]. Hence, an effective strategy is increasing HIF-1α degradation by targeting the signalling molecules to inhibit the spread of tumour cells. Although conflicting results, a study by Schwartz et al., found that translational inhibitor PX-478 sensitized PDA cells to radiation, both in vitro and in vivo; while observing decreased protein translation in hypoxia [45-47]. Moreover, HIF-1α inhibitors combined with Gem may trigger Gem-induced immune responses, causing immunogenic cell death in PDA cells [48]. In summary, HIF-1α is a promising TME therapeutic candidate for the successful management of PDA malignancy due to its diverse role in tumour progression.

Targeting MMP in the TME

MMPs are a class of zinc-dependent endopeptidases implicated in the dissemination of tumours by the enzymatic re-modelling of ECM components and enhancing angiogenesis [49]. MMPs are secreted as latent zymogens by cells and activated through proteolysis in the ECM. Downstream targets of MMP undergo proteolytic modulation, impacting cell motility, production of autonomous proteins, and alteration of signalling molecule activity harnessing an aggressive TME [50].

Experimental studies commonly use MMPs as diagnostic biomarkers for clinical responses, where decreased MMP levels are considered crucial indicators of anti-tumour response. Batimastat (MMP inhibitor) treatment of mice with orthotopic PDA in pre-clinical experiments demonstrate decreased tumour growth, metastasis, and mortality compared to the control groups, and increased Gem sensitivity, enabling a manageable course of treatment [26,51]. This demonstrates the potential MMP inhibitors hold to provide therapeutic relief in patients with PDA. With an increased understanding of the role MMPs play in PDA progression, inhibiting MMPs is a promising avenue for future therapeutics [26].

While MMP inhibition is conceivable, it has primarily been established in several broad-spectrum drugs [52]. Current research focuses on endogenous inhibitors of MMPs, known as tissue inhibitors of metalloproteases (TIMPs), which aid in maintaining the ECM by binding to MMPs to block their activity. A study conducted by Bloomston et al. demonstrated a correlation between TIMP-1 upregulation and decreased PDA cell implantation, growth, metastasis, and angiogenesis, while also enhancing tumour apoptosis [53]. In addition, TIMP-1 expression? was found to improve tumour cell sensitivity to multiple anticancer drugs via activation of downstream pathways. Specifically deactivating the mitogen-activated protein kinases (MAPK) and phosphatidylinositol 3-kinase protein kinase B (PI3K-Akt) signalling increased cancer cell sensitivity toward chemotherapy [53,54]. These findings propose a novel approach to research the potential of the TME, specifically TIMP-1, for therapeutic applications.

Targeting TGF-β Pathways in the TME

TGF-β operates as a tumour suppressor in the early stages of carcinogenesis by inducing cell cycle arrest and apoptosis, playing a vital role in cancer suppression [55]. Canonical TGF-β signalling triggers the downstream transcription of genes associated with SMAD4, an essential protein in antitumour immunity [24,56]. However, mutations in the TGF-β signalling system are frequent in PDA and contribute to tumorigenicity. For example, more than 60% of PDA patients had lost chromosome 18q21 containing the SMAD4 gene which has been associated with metastasis, according to research by Hahn et al [57]. Moreover, TGF-β is a well-known inducer of SMAD pathways, which when mutated promotes aberrant SMAD signalling and EMT (epithelial-to-mesenchymal transition), thus being an effective target to downregulate for in the TME [58,59].

Some therapeutic strategies are SMAD-independent, including (1) small-molecule kinase inhibitors (smKIs); (2) neutralizing monoclonal antibodies (mAbs); and (3) antisense oligonucleotides (AON) for anti-tumour effects. Currently, smKIs are in preclinical studies that investigate whether downregulating TGF-β would decrease malignant behaviour. For example, studies have shown galunisertib (LY2157299) demonstrates anti-tumour activity through TβR kinase inhibition, promoting T-cell infiltration into the

tumour, and triggering tumour cell death [60]. The observations of tumour suppressive activity over the course of treatment with LY2109761 and of targeting TβR kinases I/II show promising pathways for further research.

Furthermore, mAbs against TGF-β are also currently being designed. Primarily, a human IgG4 monoclonal antibody called fresolimumab (GC1008), which recognizes all TGF-β isoforms, has demonstrated acceptable safety and antitumor activity in phase 1 and 2 clinical trials for patients with malignant melanoma and breast cancer [61,62]. The anti-tumour therapeutic effectiveness of GC1008 demonstrated a reduction of tumour cell proliferation, angiogenesis, and migration. Although GC1008 has yet to be tested on patients with pancreatic cancers, the current use in advanced solid tumours may hold potential for its application to PDA.

Moreover, AON therapies, including those based on antisense RNAs, small interfering RNA (siRNA), and microRNA (miRNA), are potential treatments for PDA as they can target specific mRNAs and disrupt gene expression of TGF-β. Trabedersen (AP12009) is a phosphorothioate AON that selectively inhibits TGF-β-2 mRNA [63-65]. Preclinical experiments of AP12009 showed increased cell viability due to a reduction in TGF-β-2 secretion in vitro and xenografts, demonstrating that lowering TGF-β-2 improved therapeutic efficacy [64]. The development of the AON AP12009 targeting TGF- β-2 is a novel strategy for the downregulation of TGF-β as a promising PDA treatment [66].

Discussion

Despite substantial advances in the development of new therapeutics and understanding of PDA genetics, cytotoxic chemotherapy and surgery continue to be the principal approaches in treatment. Recent years have seen an increase in the interest around targeting various components of the TME with some notable advances in antiangiogenic treatment, including investigating the hypoxic regions, MMPs, and TGF-β signalling pathways, each of which have potential therapeutic abilities.

This review aimed to highlight the significance of understanding the complex TME components' multifaceted functions in tumour progression to expand the pool of potential therapeutic targets. Beyond the scope of the initial examination, this research may also be utilized to answer a few other open questions, like whether developing treatment options targeting the TME applies to other aggressive malignancies. With the ongoing studies into selectively targeting PDA TME, we can reduce the burden of acquired resistance and metastasis by providing novel treatment options.

Through extensive research, there were several different pathways implicated in PDA. Inhibition of these pathways must be further researched to gain insight into the links between PDA and the activation/deactivation of signalling pathways to better understand the TME targets [67]. However, there are also limitations in investigating the multicellular process involving the hypoxic TME, MMPs, and TGF-β to treat PDA.

While focusing on the hypoxic TME has shown to be an important factor in reducing tumour survival and invasiveness, developing primary inhibitors of HIFs like HAPs pose limitations. A barrier to the downregulation of hypoxic zones is the absence of inhibitor specificity, which increases resistance and decreases bioavailability by preventing binding [46,68]. This is further supported by research showing that HIF-1 has been shown to rapidly degrade by the ubiquitin-proteasome system under normoxic conditions with a narrow therapeutic window of fewer than 8 minutes [69,70]. To mitigate this, improving the pharmacokinetic properties of HIF- 1 inhibitor through modifications of shape has shown minimal success [36,71]. Other methods to increase half-life are through improved drug delivery systems, such as nanoparticle carriers, liposomes, and carbon nanotubes, have shown improved results in exploiting HIF-1 mRNA [20,72]. Therefore, determining methods to overcome challenges presented by the hypoxic TME offers a theoretical framework for further studies to improve treatment outcomes.

Furthermore, MMPIs are important for cancer therapy due to their role in inhibiting ECM degradation but inherent limitations with specific target selectivity warrant further research. First-generation MMPIs, like Batimastat, were created to specifically target the MMP catalytic site, which is similar in all MMP family members. This strategy produced a broadly-acting class of drugs effective at inhibiting MMP-mediated proteolysis but lacking the capacity to target specific MMP(s). Current efforts focus on MMPI selectivity to solely block MMPs' harmful functions outside of the catalytic domain (exosites) [73,74]. Additionally, using TIMPs to decrease cancer cell invasion has revealed drawbacks when employing MMPs in cancer therapy. Since MMPs and TIMPs exist in a stoichiometric 1:1 ratio, overexpressing TIMPs can present a negative imbalance and increase the frequency of cancer cells with unfavourable cytogenetic properties because of hypermethylation of the TIMP promoter [54,75]. Therefore, exploiting TIMPs as a therapeutic target in the PDA TME depends on further research into determining the ideal TIMP/MMP balance required for normal cell homeostasis.

Lastly, among the molecular pathways driving tumorigenesis in advanced PDA, TGF-β is known as a major regulator of cellular proliferation in PDA [61]. TGF-β works as an effective tumour suppressor in healthy cells but operates as a tumour promoter and promotes an aggressive phenotype in cancerous cells [61]. Since, PDA patients overexpress TGF-β, inhibitors and antagonists are anticipated to play a significant role in therapeutic care. Unfortunately, the systemic suppression of TGF-β might have unintended side effects as it has strong pleiotropic properties that impact both cancerous and healthy tissues [70]. For example, in later stages, hyperactivation of the

TGF-β signalling activates SMAD pathways promoting tumorigenicity [73,75]. As a result, further research in underlying molecular pathways through which TGF-β signalling regulates both normal and abnormal activities are necessary.

While there is great potential in exploiting the TME to develop therapeutic interventions, there are also limitations. Firstly, most research done in PDA is preliminary due to the disease complexity and failure in laboratory settings, demonstrating significant knowledge gaps. Several studies presented limited views of the subject rather than considering the holistic relationship between PDA and the TME; for example, sole usage of cancer cells as opposed to co-cultures. Thus, preclinical systems that allow for tumour-TME interaction would enable the interrogation of targets in a setting more representative of PDA in patients. These could be done using patient-derived organoid (PDO) models in culture with elements of the TME, such as cancer-associated fibroblasts (CAFs) or immune cells. Nonetheless, all preclinical studies provide a learning opportunity into what elements in PDA disease biology may be appropriate and suitable targets for future development in hopes of bettering the current dismal prognosis for patients.

Conclusions

Despite the poor prognosis for patients, research into the complex etiology and mechanisms has greatly advanced in recent years. Notably, the intricacy of PDA TME may present several opportunities for therapeutic investigation. Therapeutic benefits can be aimed at inhibiting certain elements of the TME, such as the hypoxic conditions, MMPs, and TGF-β pathways, while optimizing dual treatments with chemotherapeutics. In this review, accumulating evidence has suggested that targeted therapy in the PDA TME is not thoroughly investigated and requires more study to assess its feasibility in patients. However, it is understood that breaching the TME barrier presents an effective strategy to improve the delivery and efficacy of cytotoxic drugs in the future. In conclusion, the future of PDA therapy continues to be further developed and optimized through ongoing cutting-edge research, but there is still much to learn.

List of Abbreviations Used

PDA: pancreatic ductal adenocarcinoma
Gem: gemcitabine
mFFX: modified folfirinox
ICB: immune checkpoint blockade
TGF-β: transforming growth-factor-β
MMP: matrix metalloproteinases
TIMP: tissue inhibitors of metalloproteases
FDA: Food and Drug Administration
TME: tumour microenvironment
HIF: hypoxia-inducible factors
HAPs: hypoxia-activated prodrugs
ECM: extracellular matrix
MMPI: matrix metalloproteinase inhibitors
CAFs: cancer-associated fibroblasts
Br-IPM: bromo-isophosphoramide
VEGF: vascular endothelial growth factor
MAPK: mitogen-activated protein kinases
P13K-Akt: phosphatidylinositol 3-kinase protein kinase B
EMT: epithelial-to-mesenchymal transition
PDO: patient-derived organoid
smKI: small-molecule kinase inhibitors

Conflicts of Interest

The author declares no conflicts of interest.

Ethics Approval and/or Participant Consent

This study did not require ethics approval or participant consent since it is a literature review and did not involve humans, animals, or tissues in its completion.

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