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Review

Pancreatic stellate cells and pancreas cancer: Current perspectives and future strategies

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Abstract ***Background:*** Pancreatic ductal adenocarcinoma (PDAC) is a highly malignant disease with a very poor prognosis. To date patient outcomes have not improved principally due to the limited number of patients suitable for surgical resections and the radiation and chemotherapy resistance of these tumours. In the last decade, a failure of conventional therapies has forced researchers to re-examine the environment of PDAC. The tumour environment has been demonstrated to consist of an abundance of stroma containing many cells but predominantly pancreatic stellate cells (PSCs). Recent research has focused on understanding the interaction between PSCs and PDAC cells *in vitro* and *in vivo*. It is believed that the interaction between these cells is responsible for supporting tumour growth, invasion and metastasis and creating the barrier to delivery of chemotherapeutics. Novel approaches which focus on the interactions between PDAC and PSCs which sustain the tumour microenvironment may achieve significant patient benefits. This manuscript reviews the current evidence regarding PSCs, their interaction with PDAC cells and the potential implication this may have for future therapies.

Methods: A PubMed search was carried out for the terms 'pancreas cancer' OR 'pancreatic cancer', AND 'pancreatic stellate cells', NOT 'hepatic stellate cells'. All studies were screened and assessed for their eligibility and manuscripts exploring the relationship between PSCs and PDAC were included. The studies were subdivided into *in vitro* and *in vivo* groups.

Results: One hundred and sixty-six manuscripts were identified and reduced to seventy-three *in vitro* and *in vivo* studies for review. The manuscripts showed that PDAC cells and PSCs interact with each other to enhance proliferation, reduce apoptosis and increase migration and invasion of cancer cells. The pathways through which they facilitate these actions provide potential targets for future novel therapies.

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Conclusion: There is accumulating evidence supporting the multiple roles of PSCs in establishing the tumour microenvironment and supporting the survival of PDAC. To further validate these findings there is a need for greater use of physiologically relevant models of pancreatic cancer *in vitro* such as three dimensional co-cultures and the use of orthotopic and genetically engineered murine (GEM) models *in vivo*.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer related death worldwide [1]. It is a cancer with a poor prognosis and documented one year survival rates are 13% and five year survival rates as low as 2% [1]. The poor survival for pancreatic cancer (PC) is related to the lack of symptoms which results in patients with advanced disease presenting late, frequently with metastatic disease. In addition, only 10% of patients are suitable for potentially curative surgical resection at presentation and the remainder exhibit resistance to traditional chemotherapeutic agents.

Unlike many tumours where significant advances have been made and new treatment modalities developed, conventional and targeted therapies for PDAC consistently fail to produce the anticipated progress and promising basic research does not translate into the clinical setting. Currently, the mainstay of treatment for PDAC or metastatic pancreatic cancer would include single agent gemcitabine, folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) or gemcitabine-nab Paclitaxel and the choice would be dependent on the patient's fitness and performance status. Gemcitabine was approved in 1997 by the Food and Drug Agency (FDA) following a randomised phase III clinical trial which demonstrated that gemcitabine-treated patients had better clinical outcomes, with increased median survivals compared to 5-fluorouracil (5-FU) treated patients of 5.65 and 4.41 months respectively ($P = 0.0025$) [2]. The survival rate for gemcitabine at one year is 18% compared to 2% for 5-FU [3]. The most significant survival benefit has been reported with the FOLFIRINOX (oxaliplatin, irinotecan, leucovorin and 5-fluorouracil) regimen in patients with metastatic PDAC where the median survival when compared with gemcitabine is 11.1 versus 6.8 months [4]. However FOLFIRINOX treatment is associated with significant levels of toxicity and is currently reserved for patients with a good performance status.

In the last decade, scientists and researchers have turned their attention to the environment surrounding and influencing PDAC cells, instead of focusing solely on the cancer cells. This cellular microenvironment consists of an abundance of stroma which is a unique characteristic of PDACs (desmoplasia) and precursor pathologies such as chronic pancreatitis. This important characteristic of PDAC has not previously been replicated in the pre-clinical experimental models traditionally used to test chemotherapeutic agents. This may explain the failure in translating effective treatments examined *in vitro* and in animal studies to the clinical setting, since the experimental models do not accurately replicate the interactions that occur in this microenvironment in humans.

Researchers have demonstrated that the tumour microenvironment for PDAC is composed of myriad components including pancreatic stellate cells (PSCs), endothelial cells and immune and endocrine cells interacting with each other and the cancer cells in a complex fashion. PSCs have been shown to be predominately responsible for the fibrosis which is a hallmark of the PDAC microenvironment [5]. As a result PSCs and their interaction with cancer cells and other cells of the tumour microenvironment have become the focus of PDAC research.

2. Methods

Using the database PubMed/Medline a literature search for 'pancreas cancer' OR 'pancreatic cancer', AND 'pancreatic stellate cells', NOT 'hepatic stellate cells' was performed. All the studies obtained were screened for their eligibility and limits applied included journal articles and preclinical and clinical studies from the last ten years written in English with full text available. The articles were divided into those which studied the effects of pancreatic stellate cells on pancreas cancer cells and vice versa *in vitro*, *in vivo* and in clinical studies. Exclusions were applied to review articles and discussion/consensus papers. The outcomes measured included proliferation, apoptosis, invasion, metastasis, angiogenesis, hypoxia, chemoresistance and the tumour microenvironment.

3. Results

One hundred and sixty-six studies were identified from PubMed database. After applying limits and excluding reviews and irrelevant papers, 73 manuscripts were examined and included in this review as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [6]. The manuscripts were further subdivided into *in vitro* (Table 1) and *in vivo* (Table 2) studies. Studies performed *in vitro*

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