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Review

The role of pancreatic stellate cells in pancreatic cancer

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ABSTRACT

Background: The prognosis of pancreatic cancer remains desperately poor, with little progress made over the past 30 years despite the development of new combination chemotherapy regimens. Stromal activity is especially prominent in the tissue surrounding pancreatic tumours, and has a profound influence in dictating tumour development and dissemination. Pancreatic stellate cells (PaSCs) have a key role in this tumour microenvironment, and have been the subject of much research in the past decade. This review examines the relationship between PaSCs and cancer cells.
Methods: A comprehensive literature search was performed of multiple databases up to March 2014, including Medline, Pubmed and Google Scholar.
Results: A complex bidirectional interplay exists between PaSCs and cancer cells, resulting in a perpetuating loop of increased activity and an overriding pro-tumorigenic effect. This involves a number of signalling pathways that also impacts on other stromal components and vasculature, contributing to chemoresistance. The Reverse Warburg Effect is also introduced as a novel concept in tumour stroma.
Conclusion: This review highlights the pancreatic tumour microenvironment, and in particular PaSCs, as an ideal target for therapeutics. There are a number of cellular processes involving PaSCs which could hold the key to more effectively treating pancreatic cancer. The feasibility of targeting these pathways warrant further in depth investigation, with the aim of reducing the aggressiveness of pancreatic cancer and improving chemodelivery.

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Introduction

Pancreatic cancer – targeting the stroma

Pancreatic cancer continues to be one of the most aggressive and devastating diseases with very few long-term survivors. Factors contributing to this poor prognosis include late clinical presentation, the increased propensity to metastasise, and the high level of resistance tumours exhibit towards chemotherapy and radiotherapy.

The most common malignant pancreatic tumour is a pancreatic ductal adenocarcinoma (PDAC), which is of exocrine origin and accounts for over 95% [1]; therefore discussion within this review is specifically centred upon PDAC. It is essential that an improved understanding is acquired regarding the underlying cellular biology and genetic interactions that contribute to the aggressiveness of the disease. The aim is to discover new molecular pathways that may be targeted with therapeutics, thereby not only improving survival outcomes in the palliative setting, but also downsizing tumours with neoadjuvant treatment that may potentially facilitate curative resection.

Tumour stroma is defined as the interstitial tissue surrounding a malignant lesion, consisting of a wide variety of inflammatory, vascular and neural components which interact with tumours resulting in a desmoplastic reaction (DR) [2] which encourages tumour invasion, metastasis, and chemoresistance [3–5]. Stromal activity is most linked with epithelial tumours (breast, prostate, ovarian, colorectal), and pancreatic cancer perhaps demonstrates the most prominent 'stromal' reaction [5]. Furthermore it has been observed that stromal reactions can precede cancer [6], confirming the importance of premalignant lesions such as pancreatic intraepithelial neoplastic lesions (PanINs).

Pancreatic stellate cells (PaSCs) are major players in the stromal 'desmoplastic' reaction (DR) associated with PDAC. Furthermore, of all the components involved in this process, PaSCs seem to have the most significant role in generating a feedback loop between the stroma and cancer, and therefore have an essential role in tumour development. This review will examine current evidence of the cellular biology surrounding the stromal microenvironment, and the key role of PaSCs in the DR.

The stromal microenvironment

Composition

The stromal components surround the central core of a malignant pancreatic ductal adenocarcinoma. The stroma is made up of a variety of distinctly different cellular substrates resulting in a dense desmoplastic reaction (DR) which accounts for up to 90% of the total tumour volume [7]. This stroma can typically be seen surrounding tumours on radiological imaging (computed tomography) in the form of ill-defined inflammatory tissue, and this suggests an interesting concept in tumour staging as large sections of "activated" stroma may be left behind following resection, which may encourage proliferation of extremely small numbers of tumour cells that may have been left in situ (R1 margin), as well as acting as a barrier to chemotherapy, hence reducing the likelihood of eliminating this residual disease with adjuvant treatment.

It was previously thought that this DR had a protective effect [8]. However it has now been shown that once the stromal elements are activated they take on promalignant attributes, and possibly even initiate carcinogenesis [3]. The DR is composed of a variety of cellular and non-cellular components, as described in Table 1. Essentially the cellular components interact with each other and the adjacent cancer cells, resulting in the deposition of an abundant extracellular matrix (ECM).

The role of the stroma in fibrosis and cancer

In the context of a normal pancreas, the stroma can be deemed a protective environment, providing crucial signalling which maintains tissue architecture and suppresses the malignant phenotype. In normal epithelial tissue, non-activated fibroblasts are the main players in the secretion and organisation of fibrous proteins, in particular type 1 collagen which constitutes 90% of protein content.

When an injury is sustained to the ECM, the classic wound healing process is activated resulting in vascular damage and the formation of a fibrin clot. Activated monocytes then differentiate into macrophages, and subsequently release various growth factors, cytokines and proteases (e.g. metalloproteinases - MMPs). This results in both angiogenesis, and most importantly fibroblast proliferation, which leads to increased deposition of ECM proteins and resultant fibrosis. Normal tissue has a feedback mechanism to maintain homeostasis and regression in fibrosis. However, as supported by clinical observation such as in cases of chronic pancreatitis and liver cirrhosis, repeated injury results in continuous ECM synthesis, and ultimately irreversible damage. This continual damage to the ECM can be viewed as an aging process, whereby basement membranes become thin, and suboptimal cross-linking of collagen occurs. This results in a weak and fragile ECM with disorganisation promoting age-related diseases such as cancer [13].

The various ECM components as highlighted in Table 1 also have a pro-tumorigenic role in their own right. Fibrous proteins such as fibronectin and laminin stimulate reactive oxygen species (ROS) production through NAPDH oxidase, resulting in increased pancreatic cancer cell survival [14]. Matricellular proteins secreted from both stromal and cancer cells have also been shown to have a key role in facilitating tumour progression through downstream signalling that results in increased proliferation and metastasis of cancer cells. They have also been shown to directly impact on aberrant ECM remodelling, further promoting the pro-tumorigenic environment in the stroma [15].

Pancreatic stellate cells

Stellate cells have been found in a variety of organ locations, including liver, kidney, intestine and spleen [16]. Pancreatic stellate cells were first isolated in 1998 by Apte et al. [17] and since then they have been shown to have a key role in health by maintaining tissue architecture through the regulation of ECM protein synthesis and degradation. In normal tissue PaSCs exist in a quiescent state, comprising 4–7% of pancreatic parenchyma [18]. These cells

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