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Review Article

Pancreatic stellate cells in pancreatic cancer: In focus

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ABSTRACT

Pancreatic stellate cells are stromal cells that have multiple physiological functions such as the production of extracellular matrix, stimulation of amylase secretion, phagocytosis and immunity. In pancreatic cancer, stellate cells exhibit a different myofibroblastic-like morphology with the expression of alpha-smooth muscle actin, the activated form is engaged in several mechanisms that support tumorigenesis and cancer invasion and progression. In contrast to the aforementioned observations, eliminating the stromal cells that are positive for alpha-smooth muscle actin resulted in immune-evasion of the cancer cells and resulted in worse prognosis in animal models. Understanding the cancer-stromal signaling in pancreatic adenocarcinoma will provide novel strategies for therapy. Here we provide an updated review of studies that handle the topic “pancreatic stellate cells in cancer” and recent experimental approaches that can be the base for future directions in therapy.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease with a dismal 5-year overall survival of still only about 5%. The lack of specific symptoms typically leads to late detection of the disease, with consequence that only 10–15% cases present at an early resectable stage. The postoperative standard approach is adjuvant chemotherapy with a moderate effect on overall survival reflected by a prolongation of the 5-year-overall survival from 20% up to 30% [1,2]. Almost 30% of the patients are diagnosed with a disease-stage that is not suitable for surgical resection but still not metastatic, also called “locally advanced”. Unfortunately, roughly 40% of the patients already initially present with distant metastasis. Today, chemotherapeutic regimens comprise three schedules chosen mainly according to the fitness of the patient, namely FOLFIRINOX, gemcitabine/nab-paclitaxel or gemcitabine monotherapy. Lately, efforts have been made to better understand the tumor biology and to improve therapeutic approaches across all stages of the disease [3].

Microscopically, pancreatic adenocarcinoma is characterized by a dense “desmoplastic reaction” (DR) that often accounts for more than half of the tumor volume, consisting mainly of the acellular extracellular matrix (ECM) component and a cellular stromal component. The cellular stromal section contains a variety of cells including cancer-associated fibroblasts, stellate cells, endothelial cells and immune cells. The pancreatic stellate cell (PSC) is a stromal cell which exists in normal pancreatic tissue in an inactive form (quiescent). Pathological conditions such as chronic pancreatitis and pancreatic cancer induce the activation of PSC. The activated PSC is responsible for the excessive fibrotic state in pancreatic pathology.

Numerous studies have linked PSC activation with cancer initiation, progression and resistance to therapy. On the other side, the depletion of cellular stroma, including the PSC population, has a negative impact on cancer immune-surveillance that is reflected in a reduced survival of genetically engineered mice. In this article, we are aiming to provide an up to date assessment of the role that PSC plays in pancreatic cancer.

Methodology

A comprehensive search of English literature was done in

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"Pubmed" to identify all the relevant articles, date of the last search was January 2017. Articles with the following words in their titles or abstracts were examined: "pancreatic stellate cell" OR "PSC" AND "pancreatic cancer" OR "pancreatic duct adenocarcinoma" OR "pancreatic adenocarcinoma".

Discussion

PSCs description and characterization

The first description of stellate cells returns back to the 19th century. Karl Wilhelm von Kupffer in 1876 described star-shaped cells containing lipid droplets in the liver, which he named "Sternzellen" (star cells) [4,5]. Kupffer assumed that the "Sternzellen" are phagocytic cells [4]. Zimmerman in the early 20th century described the same cells as dendritic perisinusoidal cells and gave them a new name "hepatic pericytes" [6,7]. Later in 1951, the Japanese anatomist Ito described the perisinusoidal lipid-containing cells and concluded that the cells can store vitamin A and linked their function to the sinusoidal tone and tissue repair and fibrosis [8].

The first description of the star-shaped cells in the pancreatic parenchyma was in 1982 [9], a morphological description using electron microscopy in pancreatic tissues in rodents and humans. In 1998 two reports described the isolation of the star-shaped cells from murine and human pancreas. Because of the morphological similarity with the hepatic stellate cells, they have been given the name "pancreatic stellate cells" [10,11].

Extra-hepatic stellate cells have been described in other sites other than pancreas including lung, spleen, kidney and colon. Collectively, they are named "The diffuse stellate cell system" [12].

PSC exists in two statuses, the quiescent and the activated:

I The quiescent status: in the normal healthy pancreas, PSCs exist in an inactive "quiescent" state and account for approximately 4–7% of the normal human pancreatic parenchyma [10,13]. Their bodies are star shaped with long cytoplasmic processes, located mainly in the basolateral aspects of the pancreatic acinar cells, encircling the acini with their processes. The cytoplasm of quiescent PSCs has a large nucleus, few mitochondria and abundant vitamin A and albumin containing fat droplets. This can be detected using their auto-fluorescence when examined with ultraviolet radiation (vitamin A in cytoplasm emits rapidly fading blue-green fluorescence upon exposure to ultraviolet radiation with a wavelength of 328 nm) and also by electron-microscopy [10,11]. The fat droplets play an essential role in maintaining the quiescent state of the PSCs. Albumin is essential for the formation of the droplets and acts as a downstream effector of a nuclear receptor protein, peroxisome proliferator activated receptor gamma (PPARγ), which blocks PSC activation [14]. Quiescent PSCs are positive for the following markers: GFAP (glial fibrillary acidic protein), desmin, vimentin and nestin (intermediate filament protein) and neuroectodermal markers: NGF (nerve growth factor) and NCAM (neural cell adhesion molecule) [10,15].

II The activated form: PSC activation is characterized by a loss of fat droplets by autophagy [16], increased proliferation, increased expression of desmin and the expression of α smooth muscle actin (α-SMA) (Fig. 1). While α-SMA is considered as a marker of PSC activation, it is not specific for PSCs, as it is also expressed by other stromal cells including myofibroblasts, smooth muscle cells and pericytes of blood vessels [13]. The activated PSCs secrete ECM components that include: collagen I, III and IV, fibronectin and laminin [15] which is a process of great relevance in injured pancreas.

The origin of the PSCs

The embryonic origin of stellate cells, in general, is an ongoing debate. Among stellate cells, the origin of the hepatic stellate cells (HSCs) is the most extensively studied and due to the morphological and transcriptional similarity of both HSCs and PSCs [17], it would be relevant here to review the pre and postnatal findings from HSCs. During embryogenesis, the hepatic diverticulum (the future hepatic parenchyma and biliary epithelium) grows into the mesenchymal tissue of the septum transversum (origin of ventral mesentery of the foregut) and the myofibroblastic mesenchymal cells are trapped between the hepatoblasts and sinusoidal endothelium [18]. Later, the mesenchymal cells show lipid droplets in their cytoplasm. In early neonatal liver, the cells that are thought to be HSCs do not yet resemble their final shape completely and contain few small lipid molecules. Five weeks postnatal, the HSCs reach their final configuration and morphology [19]. Kissov et al. figured that cells that are thought to be progenitors of HSCs co-express desmin, αSMA and cytokeratin 8 and 18, prenatal on day 12 in rats, which may point to an endodermal origin of the stellate cells and that they share a common origin with hepatoblasts [20].

Mesenchymal Stem cells (MSCs) (Fig. 2) are multipotent stem cells that can divide symmetrically (self-renewal) and asymmetrically (differentiation). They give rise to a wide spectrum of non-hematopoietic mesenchymal multi-lineages and can be easily isolated from the bone marrow, fetal liver, umbilical cord and adipose tissue [21,22]. Systemically administered MSCs are chemotactically recruited to xenograft pancreatic cancers and they are incorporated into the tumor stroma attracted by high local concentration of growth factors and other mediators that are released in the tumor microenvironment [23]. Similar observations were made when rats were grafted with bone marrow cells expressing green fluorescence protein (GFP) and chronic pancreatitis was induced in a group of them, about 7% of PSCs pool in the normal pancreas group whereas 18% in the diseased pancreas group expressed GFP reflecting the recruitment of MSCs into the diseased pancreas [24]. These observations support the hypothesis that relocated MSCs are in part the source of cancer-associated fibroblasts (CAFs) and that they give rise to at least a subpopulation of PSCs.

Although epithelial mesenchymal transition (EMT) is required in many physiological developmental steps, EMT contributes also to tumorigenesis, the wide spectrum of trans-differentiation in tumors and to metastatic and invasive tumor spread. There is evidence that cancer cells promote their own non-malignant stroma to auto-facilitate their growth and spread; transformed malignant cells can acquire a mesenchymal-like phenotype expressing desmin, vimentin and α-SMA and can camouflage like resident normal stromal cells [25]. This process should be taken into account when considering the renewing supply of stromal cells in general and of stellate cells specifically.

PSCs in cancer

PSCs are a unique type of pancreatic stromal cells that are engaged in several roles under physiological and pathological conditions. In the healthy pancreas, PSCs are involved in phagocytosis, immunity and stimulation of amylase secretion from the exocrine pancreas. *In vitro*, they have progenitor-like capabilities, possessing ATP-binding cassette G2 (ABCG2), and transform into insulin secreting cells [26–30].

During tumorigenesis, PSCs undergo transformational changes into an active myofibroblast-like phenotype, which is involved in several processes. In most of the cases, they aim to create a suitable microenvironment to facilitate cancer progression and invasion. Intriguingly, the alteration of some of these processes in animal

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