Biochimica et Biophysica Acta 1865 (2016) 123–132

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Pancreatic cancer: Current research and future directions

Marco Falasca *, Minkyoung Kim, Ilaria Casari

Metabolic Signalling Group, School of Biomedical Sciences, CHIRI Biosciences, Curtin University, Perth, Western Australia, Australia

ARTICLE INFO

Article history:
Received 29 September 2015
Received in revised form 27 December 2015
Accepted 9 January 2016
Available online 12 January 2016

Keywords:
Pancreatic cancer
Cancer metabolism
Tumour stroma
MicroRNA
Exosomes

ABSTRACT

Despite the survival rate advancements in different types of cancer in the last 40 years, the perspective for pancreatic cancer patients has seen no substantial changes. Indeed, the five year survival rate remains around 5%. Nevertheless, in the last decade we have witnessed an increased interest in pancreatic cancer biology and this has produced a substantial increment in our knowledge on pancreatic cancer progression. The big challenge is now to translate this knowledge in better outcomes for patients. The aim of this review is to describe the latest discoveries and advancements in pancreatic cancer research and to discuss future directions.

Contents

1. Introduction

Pancreatic cancer is a deadly disease, mainly because it is generally discovered very late and it is very resistant to chemotherapy and radiation therapy [1]. The most common type of pancreatic cancer (over 90%) develops from the exocrine cells of the pancreas and is named pancreatic ductal adenocarcinoma (PDAC) [2]. There are very few treatments currently available, mostly just palliative and with several side effects [3]. Since its first clinical demonstration of efficacy in 1997, gemcitabine represented for more than a decade the first-line PDAC treatment and drug of reference [1–3]. All attempts to increase the efficacy of gemcitabine with combination therapy have produced at best marginal improvements in survival, as it is the case of its combination with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib [4]. Nevertheless, very recent approaches such as polychemotherapy, or strategies leading to improved efficacy of gemcitabine, have produced some substantial improvements [5]. Indeed in 2011, phase III trial data concerning the use in advanced pancreatic cancer of a combination of folinic acid, fluorouracil, irinotecan and oxilplatin (FOLFIRINOX) showed the longest survival improvement, around 4 months, compared to gemcitabine used as a single agent (6 months survival) [5]. Consequently, despite the fact that the side effects of such an aggressive combination make this

* Corresponding author at: Metabolic Signalling Group, School of Biomedical Sciences, Faculty of Health Sciences, Curtin University, Australia.
E-mail address: marco.falasca@curtin.edu.au (M. Falasca).
URL: http://curtin.edu.au (M. Falasca).

http://dx.doi.org/10.1016/j.bbcan.2016.01.001
0304-419X/

regimen impractical in the majority of PDAC patients, FOLFIRINOX is currently an accepted standard of care for approximately 30–40% of PDAC patients [3]. Subsequently in 2013, the use of protein-bound paclitaxel (nab-paclitaxel or Abraxane) has shown better survival rates compared to gemcitabine, suggesting that PDAC is not a chemo-resistant disease and can be effectively tackled by chemotherapy. [6]. However, although both FOLFIRINOX and Abraxane are the standards of care for metastatic disease, their efficacy is limited, often leading to an improvement of quality of life rather than an effective cure of the disease. Therefore, it is imperative to find new therapeutic strategies and valid pharmacological targets to improve the grim survival prospect that oncologists have to offer to pancreatic cancer patients. The identification of molecules and proteins involved in pancreatic cancer development and progression is critical to discover novel potential targets and to develop novel and more active drugs. Here, we provide an overview of recent advancement on pancreatic cancer research that gives us a better insight in the peculiar heterogeneity and cell plasticity of this type of cancer. In this paper, that is not a comprehensive study of current research on PDAC, we review the most salient biological features of pancreatic cancer with a focus on pancreatic tumour stroma, tumour metabolism, microRNAs and exosomes.

2. Tumour heterogeneity and cancer cell plasticity

Over the last few years, there has been an increasing number of studies focused on the understanding of the molecular and biological nature of pancreatic cancer. In particular, this increased interest has led to important advances in the understanding of the genomic complexity of the disease, the importance of the tumour microenvironment, and the peculiar metabolic adaptation of pancreatic cancer cells to obtain nutrients in a hostile environment. These studies have contributed to identify the characteristics of pancreatic cancer and underlined that its two main features, although not unique to this type of cancer, are high tumour heterogeneity and elevated cancer cell plasticity. Pancreatic cancer heterogeneity can be both phenotypic and functional and can arise either among cancer cells within the same tumour or among individual PDAC tumours, making difficult any classification and identification of common therapeutic strategies. This heterogeneity is a consequence of genetic changes, a different environment and changes in cell characteristics.

Several recent studies have provided an extensive and comprehensive genetic analysis of pancreatic cancer and contributed to design the genetic landscape of pancreatic disease substantiating the concept that this is a genetic disease [7–9]. Indeed, pancreatic cancer is characterized by the successive accumulation of mutations in key oncogenes and tumour suppressor genes [10]. Once established this heterogeneous and genetically unstable disease reveals the complexity of its nature [10]. The most common genetic alteration in PDAC is the oncogene Ras that is mutated in more than 90% of tumours [11]. Similarly, around 95% of tumours have inactivation of the CDKN2 gene that encodes the p16 protein, a regulator of G1-S transition of the cell cycle [12]. Another frequent genetic modification is reported on the p53 gene that is altered in around 75% of patients [13]. Other frequently mutated or lost genes include the *SMAD4* gene (DPC4 or SMaD4) which is deleted in pancreatic carcinoma [14].

Additional heterogeneity to pancreatic cancer is given by the presence of different cell compartments. Indeed, while the bulk of the tumour is formed by "normal" cancer cells, a minority of cells possess stem cell characteristics that make this cell type potentially resistant to chemo- and radiotherapy [15]. Additional complexity and heterogeneity are provided by a dense and desmoplastic stroma composed of fibrillar elements, such as collagen and activated fibroblasts [16].

Furthermore, the complex and heterogeneous nature of pancreatic cancer is confirmed by the fact that not all pancreatic tumours have alterations in all pathways, and the key mutations in each pathway appear to differ from one cancer to another. Indeed, a genomic analysis of 24 pancreatic cancers revealed the existence of 63 genetic alterations that affect at least 12 distinct signalling pathways [7]. More recent genomic analyses of PDAC have further increased the number of genomic alteration [8,9]. The complex heterogeneity of genetic alterations in PDAC may explain why the targeted therapy is failing in PDAC. Indeed, apart from a marginal increase in survival rate in the gemcitabine plus erlotinib association, all other combinations designed to target different key signalling pathways have failed [1–4]. In addition, recent work identified a by-pass mechanism of oncogene addiction in PDAC. Indeed, it has been shown that PDAC tumour cells can survive in the absence of oncogenic Kras, and acquire alternative growth mechanisms signals involving the Yap1 oncogene [17,18].

The definition "cancer cell plasticity" refers to the extreme ability possessed by cancer cell in adopting a cellular phenotype that better adapts to a hostile environment. An example of tumour plasticity is the ability of cancer cells to undergo an epithelial to mesenchymal transition (EMT) that confers to cells a phenotype characterized by an increased motile and invasive capacity as well as a higher resistance to apoptosis [19]. Similar to normal epithelial cells during embryonic development, cancer cells can revert back to an epithelial phenotype, in precise conditions, such as after the invasion of tissues and spread to a secondary site. This process is called the mesenchymal to epithelial transition (MET). According to a recent model proposed for pancreatic cancer progression, the seeding of distant organs is a very early event and it occurs in parallel to tumour formation at the primary site [20]. This is in agreement with clinical evidence since the majority of PDAC patients have metastatic disease at the time of diagnosis [21]. Recent work has shown that EMT and stemness acquisition are tightly regulated by a hierarchical signalling network involving two antagonistic pathways, NFATc1-Sox2 and p53-miRNA200c [22]. Therefore, the molecular decision between epithelial cell preservation and conversion into a dedifferentiated cancer stem cell-like phenotype is made at the level of p53 and NFATc1 signalling activity. The plasticity to switch from one phenotype to another is determined not only by the genetic features of the cancer cells but also by the local microenvironment in the secondary site. Another example of cancer adaptability is the metabolic plasticity, a feature that refers to the adaptation of cancer cells to different environmental conditions and their ability to switch from one metabolic phenotype to another depending on nutrient availability and hostile environments [23]. A growing evidence points to a more active function of tumour metabolism, according to which the metabolic reprogramming of cancer cells is not a simple consequence of neoplastic transformation but a key driver in cancer progression. Both concepts of tumour heterogeneity and cancer cell plasticity are quintessential characteristics of PDAC tumours and are responsible for the peculiar aggressive nature of this tumour type. In addition, heterogeneity and plasticity are traits applicable to stroma, metabolism and microRNA, underlining that all these processes are tightly interconnected and so contributing to the intrinsic aggressive nature of pancreatic cancer. Given the failure of targeted therapy in PDAC, the focus is now on targeting more broad critical players of physiological functions as a more effective therapeutic strategy. Therefore, any attempt to identify a particular target in the tumour stroma or metabolism should consider the concept of cancer plasticity and the changeable nature of PDAC cells.

3. Stroma in pancreatic cancer

The malignant progression of PDAC is characterized by its diffuse fibrotic stroma (desmoplasia) that is composed of activated fibroblast, also known as pancreatic stellate cells, infiltrating immune cells, blood vessels and extracellular proteins (Fig. 1) [24]. Together with matricellular proteins such as collagen and fibronectin, several growth factors are released in the tumour microenvironment, such as transforming growth factor-β (TGFβ-1), platelet derived growth