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Review

Pancreatic ductal adenocarcinoma: From genetics to biology to radiobiology to oncoimmunology and all the way back to the clinic

Emmanouil Fokas [a,*], Eric O'Neill [a], Alex Gordon-Weeks [b], Somnath Mukherjee [a], W. Gillies McKenna [a], Ruth J. Muschel [a]

[a] Department of Oncology, Oxford Institute for Radiation Oncology, Oxford University, Oxford, UK
[b] Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death. Despite improvements in the clinical management, the prognosis of PDAC remains dismal. In the present comprehensive review, we will examine the knowledge of PDAC genetics and the new insights into human genome sequencing and clonal evolution. Additionally, the biology and the role of the stroma in tumour progression and response to treatment will be presented. Furthermore, we will describe the evidence on tumour chemoresistance and radioresistance and will provide an overview on the recent advances in PDAC metabolism and circulating tumour cells. Next, we will explore the characteristics and merits of the different mouse models of PDAC. The inflammatory milieu and the immunosuppressive microenvironment mediate tumour initiation and treatment failure. Hence, we will also review the inflammatory and immune escaping mechanisms and the new immunotherapies tested in PDAC. A better understanding of the different mechanisms of tumour formation and progression will help us to identify the best targets for testing in future clinical studies of PDAC.

Contents

* Corresponding author at: Department of Oncology, Oxford Institute of Radiation Oncology, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Headington, Oxford OX3 7DQ, UK. Tel.: +44 1865 225832; fax: +44 1865 857127.
E-mail address: emmanouil.fokas@oncology.ox.ac.uk (E. Fokas).

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1. Introduction

Pancreatic cancer constitutes the fourth leading cause of cancer mortality. Pancreatic ductal adenocarcinoma (PDAC) is the most frequent histological type and is characterised by a dismal prognosis with a 5-year survival rate of 5% [1,2]. The American Cancer Society has reported 43,920 new cases of PDAC in the US in 2012. The majority of patients are diagnosed at a late stage due to the lack of diagnostic symptoms in the early stage disease [1]. Despite the advent of new agents, the clinical outcome of patients with PDAC remains poor. Hence, there is an urgent need for a better understanding of the biological phenotype of this deadly disease. In the present article, we comprehensively review the current literature on genetics, biology, radiobiology, mouse models, metabolism, circulating tumour cells and oncoimmunology as well as the implications of the findings for the management of patients with PDAC.

2. Genetics of pancreatic ductal adenocarcinoma

PDAC is characterised by genetic alterations that induce tumourigenesis that determine the disease phenotype. Genetic mutations occur commonly in patients with PDAC and preinvasive lesions, such as pancreatic intraepithelial neoplasia (PaIN), exhibit mutations that are similar to those found in advanced disease [3]. Also, some pancreatic cancers present familial inheritance [4]. Importantly, the disease phenotype can be closely recapitulated using genetically-engineered mouse models (GEMMs) with conditional modification of the expression of genes involved in PDAC formation and progression, such as Kras and p53 [5]. These data support the notion that PDAC has a genetic aetiology.

2.1. Preinvasive lesions

Pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystadenomas (MCNs) are the three main preinvasive lesions that have been identified in the pancreas [3]. PanIN likely emerges from the Her1-positive stem cell-like cells found at the acini–ductal epithelium junction or the mature acinar cells [6]. PanIN has three different stages of progression before it gives rise to PDAC [7,8]. These are PanIN-1, PanIN-2 and PanIN-3, depending on the degree of cytological atypia of the duct lining cells. PanIN-1 presents minimal atypia with mucinous differentiation of the ductal cells, whereas PanIn-3 has marked atypia and essentially represents a carcinoma in-situ [7,8]. IPMNs stem from the mucin-producing main pancreatic duct or its branches and have cystic morphology. MCNs present an ovarian-like stromal content and have a mucinous epithelial lining. The majority of PDACs arise from PanINs, whereas IPMN- or MCN-induced PDAC only occurs sporadically.

2.2. Telomeres in pancreatic ductal adenocarcinoma

Telomeres are DNA–protein complexes that cap the chromosome ends and are made of tandem repeats of the 5′-TTAGGG-3′ sequence [9]. They have evolved by eukaryotic organisms to solve the problem of DNA end-protection. Shortening of the telomeric DNA at chromosome ends limits the lifespan of human cells and short telomeres activate the DNA damage response (DDR).

Activation of telomerase that is responsible for telomeric DNA synthesis is essential in cancer cell immortalization and cancer progression [9]. Patients with PanIN have abnormally shortened telomeres compared to the ductal epithelium of normal pancreas [10]. Also, patients with PDAC often have activation of telomerase expression and telomere dysfunction [11,12].

2.3. Pancreatic development and genetic alterations in pancreatic ductal adenocarcinoma

Early pancreatic development is mediated by Pdx1 and Ptf1a genes in conjunction with the Sonic Hedgehog (Shh) and Notch signalling pathways. The pancreatic homeobox transcription factor Pdx1 is mediated by the Shh repression and is expressed in the nascent pancreatic bud. The Pdx1 promoter has been used in GEMMs to direct transgene expression at the bud stage [13]. Ptf1a is a basic helix–loop–helix (bHLH) transcription factor present in acinar cell nuclei that is required for the development of the pancreas. Ptf1 is involved in the activation of the gene promoters that encode the secretory digestive enzymes and in pancreatic tissue development [14]. In addition, nestin, an exocrine pancreas progenitor marker and Mist1 are involved in early organ formation [15–19]. All four genes have been used as promoter in the development of GEMMs of PDAC. Two common pathways involved in pancreatic organogenesis and development are the Shh and Notch signalling pathways [6,20]. Preclinical evidence has suggested involvement of both pathways in initiation of PanIN and tumour growth. Shh is not expressed in normal adult pancreas but aberrant signalling has