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Review

A historical perspective of pancreatic cancer mouse models

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ABSTRACT

Pancreatic cancer is an inherently aggressive disease with an extremely poor prognosis and lack of effective treatments. Over the past few decades, much has been uncovered regarding the pathogenesis of pancreatic cancer and the underlying genetic alterations necessary for tumour initiation and progression. Much of what we know about pancreatic cancer has come from mouse models of this disease. This review focusses on the development of genetically engineered mouse models that phenotypically and genetically recapitulate human pancreatic cancer, as well as the increasing use of patient-derived xenografts for preclinical studies and the development of personalised medicine strategies.

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1. Introduction

Pancreatic cancer is an aggressive malignancy and represents the 4th leading cause of cancer death, with a 5-year survival rate of approximately 5% [1]. Despite a greater understanding of the molecular characteristics of this cancer, overall patient survival has not improved for several decades. Surgical resection still remains the only potential curative treatment, however at the time of diagnosis, less than 20% of patients are suitable for surgery. Treatment options are limited and largely ineffective [2,3].

Pancreatic cancer comprises several histological variants, the most common being pancreatic ductal adenocarcinoma (PDAC), which accounts for over 85% of all pancreatic malignancies. Other types of pancreatic cancers include acinar cell carcinoma, pancreatic neuroendocrine tumours and undifferentiated carcinoma. PDAC arises from well-characterised precursor lesions, the most common being pancreatic intraepithelial neoplasia (PanIN) [4,5], but also including intraductal papillary mucinous neoplasms (IPMN) [5] and mucinous cystic neoplasms (MCN) [6]. PanINs can be sub-classified into PanIN-1A, PanIN-1B, PanIN-2 and PanIN-3 based of the degree of cytological and architectural atypia and are known

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to demonstrate many of the same genetic alterations seen in PDAC, with the prevalence of these alterations increasing with the degree of PanIN [5]. Activating *KRAS* mutations represent the most common and well-characterised genetic alteration in PDAC, occurring in >95% of cases, mainly via point mutations in codon 12 [7,8]. *KRAS* mutations occur in early PanIN lesions and represent a potential initiating factor for this disease. The other most common genetic events in PDAC are inactivation of the tumour suppressors *CDKN2A* (*P16INK4A*) [9,10], *TP53* [11,12] and *SMAD4* [13] occuring in >95%, 50–75% and 55% of patients, respectively. Recent PDAC sequencing efforts have identified many other genetic alterations that occur at much lower frequencies and highlight the genetic complexity of this malignancy [14,15]. Interestingly, despite the large number of somatic mutations identified in PDAC, these alterations can be associated with 12 core signalling pathways [15].

Many genetically engineered mouse models (GEMMs) have been developed that closely recapitulate several pancreatic cancer subtypes. These models have proven useful in identifying the molecular drivers of pancreatic tumour initiation and progression as well as providing a relevant system for developing and testing novel therapeutic strategies. Xenograft models, in particular patient-derived xenografts, are also proving to be an extremely valuable tool in evaluating novel treatment strategies in the era of personalised medicine. This review provides an overview of the major pancreatic cancer GEMMs as well as highlights the increasing use of patient-derived xenograft models of pancreatic cancer.

2. Early attempts to model pancreatic cancer

Early attempts to model pancreatic cancer began in the 1980s when technologies for generating transgenic mice carrying oncogenes were developed. These early models utilised the Elastase promoter or the rat insulin promoter (RIP) to drive expression of the viral oncogene SV40 in acinar cells and β-cells of the mouse pancreas, respectively. RIP-Tag mice developed insulinomas (discussed below) and Elastase-SV40 mice developed acinar cell carcinomas [16–19]. Elastase-SV40 mice also developed islet cell tumours and somatostatin-cell hyperplasia, but did not develop PanINs or PDAC. Further attempts to produce transgenic mouse models also used the elastase promoter to overexpress human oncogenes in the mouse pancreas. In 1987, Quaife et al. overexpressed normal and mutant *H-ras* using the elastase promoter [20]. Mice expressing normal *H-ras* developed acinar cell hyperplasia and dysplasia, while the majority of mice expressing mutant *H-ras* died as newborns; those that survived were mosaic for *H-ras* and died of pancreatic tumours between 1.5 and 14 months. Overexpression of *TGF-α* in acinar cells did not induce pancreatic tumours, however mice did develop lesions resembling acinar-to-ductal metaplasia and pancreatic fibrosis, and was one of the first mouse models to suggest an acinar cell origin for PDAC [21,22]. In 1991, Sandgren et al. published an elastase-cmyc transgenic mouse model. These mice developed tumours with a mixed acinar/ductal histology between 2 and 7 months of age, however the ductal features were not observed until later stages of tumour development, and no PanINs were seen in this model [23]. In 2003, Grippo et al. overexpressed a common activating mutation of *Kras* in pancreatic acinar cells [24]. Surviving mice developed multifocal acinar cell hyperplasia and less commonly the formation of tubular complexes. In older mice, acinar to ductal metaplasia and early PanIN lesions were also observed. While no tumours developed in these mice, this model did demonstrate that activating *Kras* in acinar cells could result in the development of PDAC precursors and suggested additional genetic events may be required for pancreatic tumorigenesis.

3. Genetically engineered mouse models of pancreatic cancer

3.1. Mouse models of PDAC

Many GEMMs of pancreatic cancer have been developed and this review focusses on models that have been developed to recapitulate the most well-known genetic aberrations found in human pancreatic cancer. These models are summarised in Table 1.

3.1.1. Kras models

A breakthrough in developing GEMMs of PDAC occurred with the advent of the LSL-Kras^{G12D} mouse [25]. This mouse harbours a knockin mutant *Kras* allele containing a glycine to aspartic acid transition in codon 12, upstream of which resides a conditional STOP cassette flanked by LoxP sites, preventing expression of the mutant allele. When combined with a tissue-specific Cre recombinase, the STOP cassette is excised resulting in constitutive activation of *Kras* at physiological levels. This mutation represents the most common activating *Kras* mutation seen in human PDAC. Hingorani et al. targeted this mutation to pancreatic progenitor cells by crossing LSL-Kras^{G12D} mice with transgenic mice expressing a bacterial Cre recombinase under control of either the *Pdx1* or *Ptf1a* (*P48*) promoters [26]. The resulting mice developed the full spectrum of PanIN lesions, which progressed with age. A proportion of these mice went on to develop metastatic tumours resembling human PDAC after a long latency (>12 months). Lesions in these mice expressed similar markers to human PDAC, including the Notch signalling target Hes1, COX2 and MMP7. This model demonstrated that activation of *Kras* is sufficient to induce precursors to PDAC and in some instances progress to invasive and metastatic PDAC and has since become the backbone for the development of many other mouse models of PDAC.

One of the limitations of the LSL-Kras^{G12D}; Pdx1-Cre (also known as the KC) model is that *Kras* activation is targeted to the embryonic pancreas, with PanINs developing shortly after birth. However, PDAC occurs in older individuals through stochastic mutations in adult pancreas. Guerra et al. developed a model that allowed temporal control of *Kras* activation in the pancreas using a Tet-off system [27]. Similar to the KC model, when *Kras* was activated in the developing pancreas at E16.5, Kras+/LSL-G12VGeo; Elas-tTA/tetOCre mice developed acinar to ductal metaplasia progressing to high-grade PanINs by 12 months of age, a proportion of which went on to form PDAC after a long latency. However, activation of *Kras* in 10 day-old mice significantly delayed the formation of PanINs and reduced the incidence of PDAC. Importantly, activation of Kras in adult mice had no effect at all in acinar cells, indicating that mature acinar cells are resistant to transformation by oncogenic *Kras*. Invasive PDAC could be induced in these mice when treated with caerulein to induce chronic pancreatitis, indicating that pancreatitis increases the pool of cells susceptible to transformation by Kras^{G12V}, potentially acinar precursors. In addition, this model supports the link between pancreatitis and an increased risk of developing PDAC, and provides a valuable model for investigating the role of pancreatitis-induced inflammation in tumorigenesis.

While these models have demonstrated that targeting mutant *Kras* to the mouse pancreas is sufficient to induce PDAC in mice, the incomplete penetrance and long latency observed in these models suggested that additional genetic events could increase the incidence of tumours in mice and accelerate tumour progression. Since the generation of these *Kras*-induced PDAC models, many other models have been developed combining *Kras* mutations with other genes that are purported to be drivers of PDAC.

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