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Review

Role of angiogenesis in pancreatic cancer biology and therapy

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, and there is a close parallel between disease mortality and incidence. Malignancy is often diagnosed at an advanced stage due to the lack of early symptoms. For the majority of advanced or metastatic pancreatic cancer patients, therapeutic options are limited. Although several new chemotherapeutic regimens have been developed, the overall response rate remains low. Invasive tumour growth and distant metastasis require angiogenesis, a hallmark of cancer, and angiogenic inhibition is a valuable option for cancer therapy. Some anti-angiogenic drugs have been developed for cancer treatment. This review will focus on the role of angiogenesis and anti-angiogenic treatment strategies as well as combination therapy in pancreatic cancer. Translational information from recent molecular biology and animal studies is also summarized. Finally, the dosing schedule for bevacizumab with other chemotherapeutic protocols for pancreatic cancer treatment is discussed.

1. Introduction

PDAC is nearly always a mortal disease, with a 5-year overall survival rate slightly higher than 5% and a median survival of 6 months [1]. R0 resection remains the only possible opportunity to completely cure the disease. Unfortunately, 80–85% of patients are diagnosed with unresectable advanced illness at their first visit, and curative-intent resection is only applicable to less than 20% of patients [2]. Even after radical resection, recurrence is nearly inevitable for most patients, and the 5-year survival rate after radical surgery is 25% at best [2]. For patients with late-stage PDAC, systemic chemotherapy is the only treatment that prolongs survival and improves quality of life. Since gemcitabine was established as the first-line treatment for advanced PDAC in 1997 [3], drug regimens for late-stage PDAC have progressed slowly. In contrast to the notable success for patients with other solid tumours, targeted therapy has minimal effects on patients with locally advanced PDAC. Recently, two novel combination chemotherapies have shown promise for improving the prognosis and quality of life of PDAC patients. Compared with gemcitabine treatment, the FOLFIRINOX protocol (fluorouracil, irinotecan, folinic acid and oxaliplatin) resulted in an improved overall median survival from 6.8 to 11.1 months for metastatic PDAC [4]. In 2013, the use of gemcitabine plus nab-paclitaxel also slightly improved median overall survival (mOS) [5]. Although these two chemotherapy regimens have achieved promising results for metastatic PDAC treatment, the overall efficacy remains unsatisfactory. Target therapies are starting to emerge and have increased survival of multiple solid tumours, including melanoma and lung cancer. Numerous novel mutated genes related to PDAC have been uncovered, though effective drugs targeting these genes are not unavailable. In 1971, Folkman et al. proposed the hypothesis that tumour growth depends on angiogenesis [6], which was subsequently proven and is considered one of the hallmarks of cancer [7]. Since then, anti-angiogenic regimens have been demonstrated to be effective in multiple solid tumours, such as clear cell renal carcinoma, ovarian cancer, and cervical cancer. PDAC is characterized by an extremely high potential for invasion and metastasis, and angiogenesis plays a crucial role in this process and remains a viable target to treat PDAC. In this review, we discuss the current progress of anti-angiogenic therapies applied to PDAC (Fig. 1).

2. Effects of angiogenesis on cancer

During embryonic vasculogenesis, the process of angiogenesis involves the birth of endotheliocytes (angioblasts) predecessors and their

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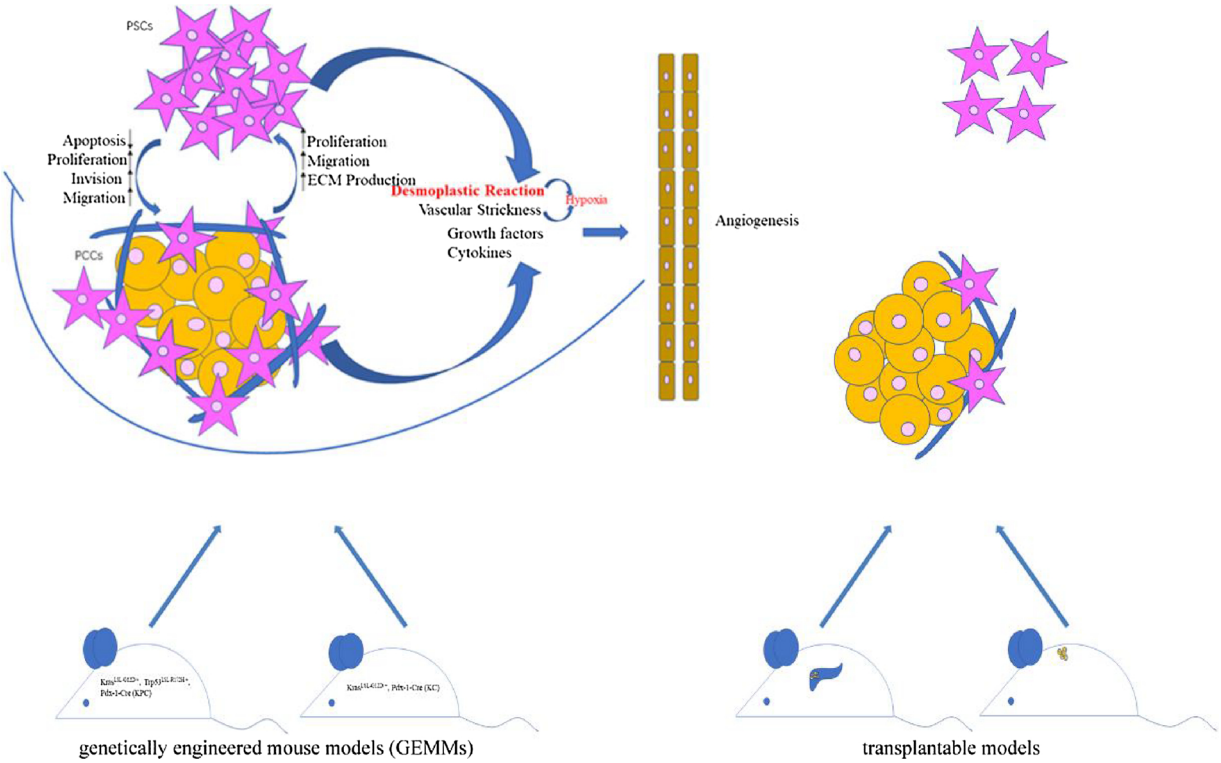

Fig. 1. Characteristics of angiogenesis and its complex interplay with PSCs and PCCs in PDAC.
Differently from the subcutaneous and orthotopic pre-clinical models that lack stroma and PCCs are close to the vessels, human PDAC and GEMMs have dense stroma, which contributes to a high interstitial pressure and collapsed vessels. Except for excessive dense extracellular matrix, PSCs and PCCs produce several angiogenic molecules and there is a crosstalk between PSCs and PCCs and their interaction finally inhibits and enhances angiogenesis.

assembly into a primary capillary plexus, from which new blood vessels emerge from pre-existing ones by sprouting and branching [8]. The vascular endothelium is normally dormant in adults, with the exception of the vasculature of the female reproductive cycle. In addition, appropriate host responses to stimuli such as wound healing activate the vasculature transiently. The clearest difference between pathological and physiologically appropriate angiogenesis is the tightly regulated balance of the “angiogenic switch”, which is regulated by numerous factors and occurs at different periods in tumour progression based on the tumour type and microenvironment [9]. In addition to vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, represent another class of regulators that directly stimulate blood vessel growth; these proteins are crucial for extracellular matrix degradation, endothelial cell migration and therefore angiogenesis [10]. Angiogenesis refers to numerous corresponding endothelial cell activities, including proliferation and migration [11,12]. It is generally accepted that angiogenesis is an important mechanism used by tumours to obtain sufficient nutritional support, such as sustenance and oxygen [13], in addition to removing carbon dioxide and metabolic waste. Moreover, angiogenesis also plays a vital role in the asymptomatic premalignant phase of neoplastic progression [14]. In the initial prevascular stage of tumour growth, the tumour is typically less than 2–3 mm [15], and oxygen and nutritional supplementation is obtained by diffusion into tumours of this size. The tumour remains in a dormant state until it becomes vascularized, which occurs when a subgroup of tumour cells switch to an angiogenic phenotype [16]. Moreover, microvessel density (MVD) is a useful prognostic indicator in several human neoplasms and is associated with biological aggressiveness and metastatic potential in numerous primary tumours. An unbalanced mix of proangiogenic signals and chronic activated angiogenesis contribute to typically aberrant blood vessels characterized by abnormal multiple branching, convoluted and excessive vessel branching, distorted and variable vessels and disrupted interendothelial junctions [14]. A large number of blood vessels increases the chance of tumour cells entering circulation and also promotes fragmentation and leaking of the neovascular basal membrane, which is more likely to be penetrated by tumour cells than mature blood vessels. Once metastatic cells arrive at their target organ, they must undergo neovascularization for the metastasis to grow to a clinically detectable size [17].

3. Characteristics of angiogenesis in PDAC

In addition to the previously discussed features identified in many cancers, PDAC is characterized by an intense fibroinflammatory response that generates extraordinarily high interstitial fluid pressures (IFP). Normally, the IFP ranges from 8 to 13 mmHg in a mouse [18], whereas the IFP ranges from 75 to 130 mmHg in the pancreas of a mouse with pancreatic cancer, which is higher than previously considered in solid tumours and results in vasculature collapse and poor small molecule delivery. The development of oncology drugs has historically relied on xenograft mouse models to test the efficacy of novel agents, and we heavily rely on preclinical research using mouse models generated from transplanted tumours. However, applicable PDAC models have demonstrated limited predictive utility in response to numerous chemotherapeutic agents, including gemcitabine [19–23]. With a deeper understanding of genetic alterations in PDAC, genetically engineered mouse models (GEMMs) have been generated that develop autochthonous tumours recapitulating human pathology [24]. These models are consistent with human PDAC samples that exhibit smaller diameter vessels and poor vasculature compared with adjacent normal human pancreas [18,25]. The inherently hypovascular character of PDAC has been reported in GEMMs, including the KrasLSL-G12D/+, Trp53LSL-R172 H/+, Pdx-1-Cre (KPC) PDAC mouse model and KrasLSL-G12D/+, Pdx- 1-Cre mice. Olive et al. and Provenzano et al. demonstrated that KPC tumours exhibit poor vasculature and perfusion as well as impaired drug delivery compared with transplant models or