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Mini-review

Overview of pre-clinical and clinical studies targeting angiogenesis in pancreatic ductal adenocarcinoma

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ABSTRACT

The importance of angiogenesis in pancreatic ductal adenocarcinoma (PDAC) and its therapeutic potential have been explored in both pre-clinical and clinical studies. Human PDACs overexpress a number of angiogenic factors and their cognate high-affinity receptors, and anti-angiogenic agents reduce tumor volume, metastasis, and microvessel density (MVD), and improve survival in subcutaneous and orthotopic pre-clinical models. Nonetheless, clinical trials using anti-angiogenic therapy have been overwhelmingly unsuccessful. This review will focus on these pre-clinical and clinical studies, the potential reasons for failure in the clinical setting, and ways these shortcomings could be addressed in future investigations of angiogenic mechanisms in PDAC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC), which comprises >85% of pancreatic cancers, is the 4th leading cause of cancer death in the United States with a 1- and 5-year relative survival of 28% and 7%, respectively [1–3]. These statistics are largely due to advanced stage at clinical presentation, the high frequency of major driver mutations, marked resistance to chemotherapy and radiation, and extensive desmoplasia that impedes drug delivery [4–8]. Because advances in screening, prevention, and treatment are limited compared to other cancers, PDAC is now projected to surpass breast, prostate, and colorectal cancers to become the second leading cause of cancer death by 2030 [9].

At presentation, only 15–20% of patients are eligible for surgical resection, the only chance for cure [1–3]. Even then, outcomes are poor, with a 5 year survival between 20 and 25% post-resection, since most of these patients develop disease recurrence [10]. Therefore, chemotherapy is recommended as adjuvant treatment for those undergoing surgical resection and is the mainstay of treatment for patients with locally advanced or metastatic disease [2]. The current standard of care for patients with metastatic disease includes gemcitabine plus nab-paclitaxel or fluorouracil plus leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) [2,11].

Angiogenesis

Blood vessel growth throughout adult life is primarily achieved via angiogenesis [12–18]. However, the adult vasculature is mostly

Abbreviations: ANGPT, angiopoietin; BRAF, serine/threonine-protein kinase B-raf; CAF, cancer associated fibroblast; Cdkn2a, cyclin-dependent kinase inhibitor 2A; CI, confidence interval; CSF1R, macrophage colony-stimulating factor 1 receptor; DLL4, delta-like protein 4; EC, endothelial cell; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; FGF, fibroblast growth factor; FGF2, fibroblast growth factor 2; FGFR-1, fibroblast growth factor receptor 1 (gene: FGFR1); FOLFIRINOX, fluorouracil plus leucovorin, irinotecan, and oxaliplatin; GEMM, genetically engineered mouse model; Gpc1, glypican-1; HIF-1α, hypoxia inducible factor 1, alpha subunit (gene: HIF1A); HR, hazard ratio; HRG, heregulin (gene: NRG1); HSPG, heparan sulfate proteoglycan; I, immune cell; IHC, immunohistochemistry; IL-8, interleukin-8 (gene: CXCL8); KC, $Kras^{LSL\text{-}G12D/+}$, Pdx-1-Cre; KIC, $Kras^{LSL\text{-}G12D/+}$, $Cdkn2a^{LoxP/LoxP}$, Pdx-1-Cre; KPC, $Kras^{LSL\text{-}G12D/+}$, $Trp53^{LSL\text{-}R172H/+}$, Pdx-1-Cre; Kras, Kirsten rat sarcoma viral oncogene homolog; MVD, microvessel density; NCI, National Cancer Institute; NICD, notch intracellular domain; NIH, National Institutes of Health; NRP1, neuropilin-1; ORR, objective response rate; OS, overall survival; PCC, pancreatic cancer cell; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PDGFRB, platelet-derived growth factor receptor beta; PFS, progression free survival; PlGF, placenta growth factor (gene: PGF); RNA-Seq, RNA sequencing; SCFR, mast/stem cell growth factor receptor Kit (gene: KIT); TCGA, The Cancer Genome Atlas; TGF-β, transforming growth factor beta (gene: TGFB1); Trp53, transformation related protein 53; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor A (gene: VEGFA); VEGF-B, vascular endothelial growth factor B (gene: VEGFB); VEGFA, vascular endothelial growth factor A (protein: VEGF-A); VEGFR, vascular endothelial growth factor receptor; VEGFR-1, vascular endothelial growth factor receptor 1 (gene: FLT1); VEGFR-2, vascular endothelial growth factor receptor 2 (gene: KDR); VEGFR-3, vascular endothelial growth factor receptor 3 (gene: FLT4).

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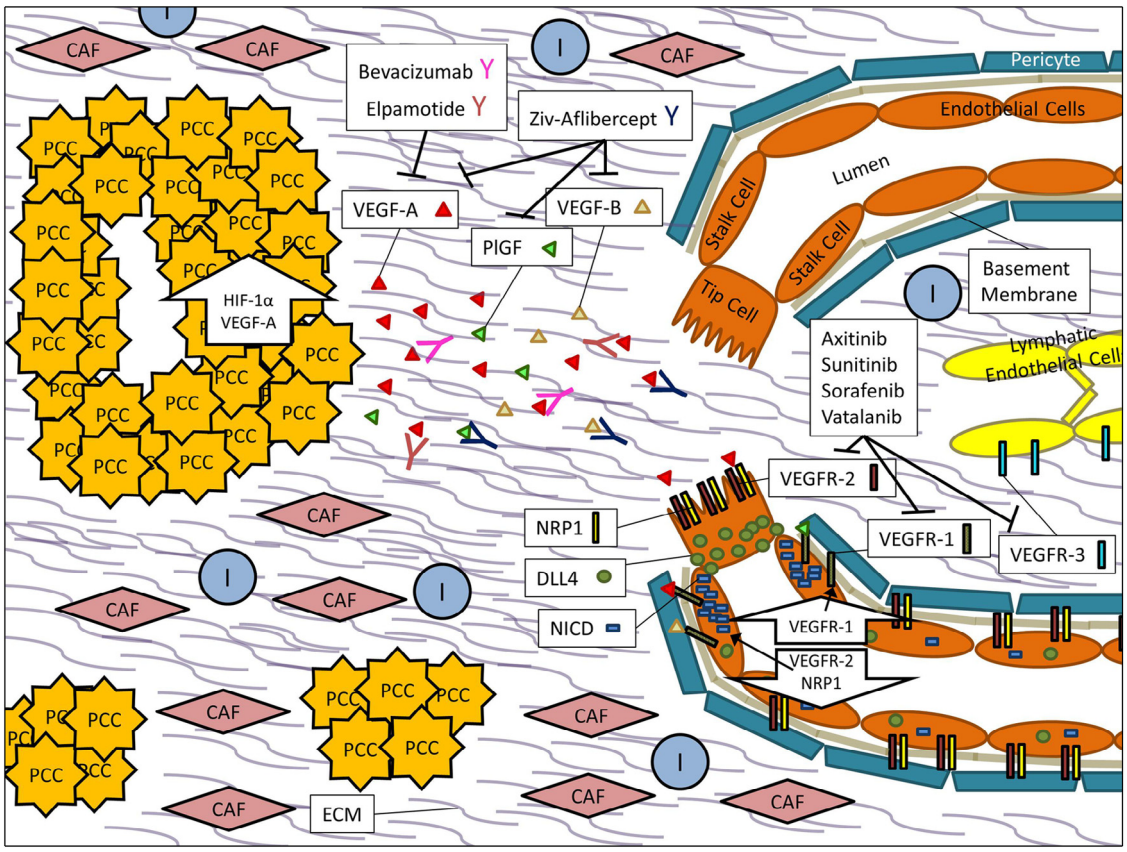

Fig. 1. PDAC angiogenesis. In PDAC, pancreatic cancer cells (PCCs) proliferate within a desmoplastic stroma that consists of both cellular components such as cancer associated fibroblasts (CAFs), immune cells (Is), and endothelial cells (ECs) as well as extracellular matrix (ECM) components like soluble growth factors, cytokines, collagens, fibronectin, laminin, glycoproteins, and proteoglycans. Up-regulation of hypoxia inducible factor 1, alpha subunit (gene: HIF1A) (HIF-1α) and the pro-angiogenic molecule VEGF-A within PCCs results in secretion of VEGF-A molecules into the tumor microenvironment. When VEGF-A signals through VEGFR-2 and its NRP1 co-receptor on endothelial cells, downstream signaling results in increased expression of DLL4. DLL4 will bind to Notch receptors on neighboring cells, subsequently releasing NICD, which then down-regulates VEGFR-2 and NRP1 expression and up-regulates expression of the VEGFR-1 decoy receptor. This favors migration of a tip cell toward the VEGF-A gradient while the neighboring stalk cells become de-sensitized to the signal. In the quiescent vasculature, DLL4 and Notch signaling are balanced. Small molecule inhibitors of angiogenesis, such as Axitinib, Sunitinib, Sorafenib, and Vatalanib primarily act on the vascular endothelial growth factor receptor complexes (VEGFR-1, VEGFR-2, and Vascular endothelial growth factor receptor 3 (gene: FLT4) (VEGFR-3)), while recombinant protein inhibitors of angiogenesis like Bevacizumab, Elpamotide, and Ziv-Aflibercept act on vascular endothelial growth factor ligands like VEGF-A, vascular endothelial growth factor B (gene: VEGFB) (VEGF-B), and/or placenta growth factor (gene: PGF) (PlGF).

quiescent as only 0.01% of the endothelium undergoes cell division at any time [12,13,15,17,18]. Examples of physiological angiogenesis in the adult include wound healing, tissues undergoing growth, exercise induced angiogenesis in heart and skeletal muscle, the hair cycle, skeletal growth, and female reproductive processes. Pathological examples include intraocular neovascular disorders, infantile hemangiomas, immunogenic rheumatoid arthritis, psoriasis, and tumorigenesis [12,13,16–20].

Through the use of models like the mouse retina, which becomes vascularized postnatally, we now understand many of the key players and processes involved in physiological angiogenesis [21]. In general, activation of endothelial cells by pro-angiogenic molecules leads to the detachment of pericytes from the endothelium and remodeling of the basement membrane and cell-to-cell junctions (Fig. 1) [22]. The best known pro-angiogenic molecule is vascular endothelial growth factor A (gene: VEGFA) (VEGF-A). VEGF-A binds to vascular endothelial growth factor receptor 2 (gene: KDR) (VEGFR-2) on endothelial cells, and its signaling is enhanced by the neuropilin-1 (NRP1) co-receptor, which facilitates complex internalization (Fig. 1) [22]. Downstream signaling results in increased expression of the Notch ligand delta-like protein 4 (DLL4), which binds to Notch receptors on neighboring endothelial cells (Fig. 1) [22]. This releases the notch intracellular domain (NICD) in these cells, which down-regulates VEGFR-2 and NRP1, and up-regulates vascular endothelial growth factor receptor 1 (gene: FLT1) (VEGFR-1), a decoy receptor for VEGF-A (Fig. 1) [22].

The goal of this process is to isolate one cell that will migrate toward the pro-angiogenic gradient (called the tip cell) while de-sensitizing neighboring cells to the same signal. It is believed that DLL4 and Notch signaling are balanced in the quiescent vasculature, and that tip cells will offset the balance in response to pro-angiogenic signals [14]. The cells adjacent to the tip cell are called stalk cells, and they proliferate behind the tip cell to elongate the sprout and form a lumen (Fig. 1) [22]. Once two tip cells on different sprouts meet, they will anastomose to form a perfused branch (Fig. 1) [22]. Basement membrane then forms, and pericytes are recruited to cover the vessel (Fig. 1) [22]. The process is dynamic in that endothelial cells will compete for the tip position with different cells displaying the phenotype over time.

Tumor angiogenesis

Whereas physiological angiogenesis is tightly controlled and comes to a resolution, pathological angiogenesis is abnormal and does not resolve [13,16,17,20,21]. Because cells need nutrients and oxygen from nearby capillaries to function and survive, early tumor growth is often restricted to a volume of only a few cubic millimeters until it is able to switch to an angiogenic phenotype [13,16,17,19,20,23,24]. Activation of angiogenesis occurs when pro-angiogenic molecules predominate over anti-angiogenic molecules, whereas inactivation occurs when the anti-angiogenic molecules dominate [12,13,25].

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