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Review

Mechanisms of resistance to anti-angiogenesis therapies

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ABSTRACT

Angiogenesis, the formation of new blood vessels from preexisting ones, provides oxygen and nutrients to actively proliferating tumor cells. Hence, it represents a critical aspect of tumor progression and metastasis. Because inhibition of angiogenesis represents a major approach to cancer treatment, the development of inhibitors of angiogenesis is a major challenge. The first FDA approved anti-angiogenic drug bevacizumab, a humanized monoclonal antibody directed against the Vascular Endothelial Growth Factor (VEGF), has been approved for the treatment of metastatic colorectal, lung, breast, and kidney cancers. The encouraging results have lead to the development, in the past few years, of other agents targeting angiogenic pathways as potent anti-cancer drugs and a number of them have been approved for metastatic breast, lung, kidney, and central nervous system cancers. Despite a statistically significant increase in progression free survival, which has accelerated FDA approval, no major benefit to overall survival was described and patients inevitably relapsed due to acquired resistance. However, while progression free survival was increased by only a few months for the majority of the patients, some clearly benefited from the treatment with a real increase in life span. The objective of this review is to present an overview of the different treatments targeting angiogenesis, their efficacy and the mechanisms of resistance that have been identified in different cancer types. It is essential to understand how resistance (primary or acquired over time) develops and how it may be overcome.

1. Introduction

1.1. Mechanism of action of anti-angiogenesis drugs

Under physiological conditions, angiogenesis is a finely controlled mechanism that is the result of a dynamic balance between pro- and anti-angiogenic factors. Physiological angiogenesis normally takes place during embryonic development, wound healing and the female reproductive cycle. Under pathological conditions, angiogenesis contributes to numerous pathologies including: ischemic, inflammatory, infectious and immune disorders. Angiogenesis is required to support the growth of a tumor beyond the size of about 1–2 mm^3. Tumors secrete chemical signals that induce angiogenesis and/or stimulate nearby normal cells to produce angiogenic signaling molecules. The resulting new blood vessels provide growing tumors with oxygen and nutrients, thereby allowing the cancer cells to invade nearby tissues, and to form metastases. Since most tumors cannot grow without a blood supply, the idea was to find ways to block tumor neo-vascularization in order to "asphyxiate" it. Inhibitors of angiogenesis are designed to block the formation of new blood vessels, to prevent the growth of the tumor and the development of metastases. Some of these agents have been associated with existing chemotherapy regimens, whereas others are used as single agents. Inhibitors of angiogenesis are currently thought to act on three major steps of the angiogenic signaling pathway.

1.1.1. Inhibition of the growth factors secreted by tumor cells to stimulate the proliferation of endothelial cells

Given the complexity of a process such as angiogenesis, it is important to note that VEGF is a predominant player in both physiological and pathological angiogenesis: VEGF signaling is one of the main ways of activating and/or recruiting pro-angiogenic cells.

Abbreviations: AKT/PKB, protein kinaseB; BMDCs, bone marrow-derived cells; BVZ, bevacizumab/Avastin; CSC, cancer stem-like cells; EGF, epidermal growth factor; EPC, endothelial progenitor cells; GIST, gastro-intestinal stromal tumor; mTOR, mammalian target of rapamycin; OS, overall survival; PDGF, platelet-derived growth factor; PFS, progression free survival; PPC, pericyte progenitor cells; PTEN, phosphatase and tensin homolog; RCC, renal cell carcinoma; RTK, receptor with a tyrosine kinase; TAF, tumor-associated fibroblast; TAMs, tumor-associated macrophages; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VHL, von Hippel–Lindau.

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The biology of the VEGF protein (also known as VEGF-A) is complex. Major pro-angiogenic isoforms resulting from alternative splicing (VEGF 206, 189, 183, 165, 162, 148, 145, 121, 111) [1] stimulate angiogenesis in health and disease by signaling mainly through trans-membrane VEGF receptors-1 and 2 (VEGFR-1 and VEGFR-2). The production of VEGF can be disproportionately up-regulated in tumors via hypoxia or loss of tumor suppressors like PTEN (Phosphatase and TENsin homolog) and Von Hippel–Lindau (VHL) [2,3]. Furthermore, Ras and RAF oncogenes up-regulate VEGF expression and therefore promote indirectly tumor growth by stimulating angiogenesis [4–6]. VEGF is secreted not only by tumors cells but also by tumor-associated stromal cells, which stimulate vascular growth to supply the oxygen and nutrients required for tumor growth and tumor cell dissemination. The inhibition of angiogenesis by blocking VEGF signaling has been investigated in the treatment of patients with solid tumors. The first inhibitor of angiogenesis approved by the FDA was bevacizumab/Avastin (BVZ), a humanized monoclonal antibody targeting VEGF. It was initially approved for use with chemotherapy in metastatic colorectal cancer [7], but is now used together with chemotherapy for metastatic non-squamous non-small cell lung cancer [8] and with interferon-alpha to treat metastatic Renal Cell Carcinoma (RCC) [9]; as a single agent for treatment of recurrent GlioBlastoma Multiform (GBM) [10,11]. Recently, two phase III trials (GOG218, ICON 7) showed that BVZ in combination with carboplatin and paclitaxel prolonged PFS of women with epithelial ovarian cancer [12,13]. These results led to the approval of these combinations for women with advanced ovarian cancers. BVZ inhibits the interaction between VEGF and its receptors and thus their subsequent activation. Clinical trials have demonstrated that, although monotherapy with BVZ is largely inefficient, a number of preclinical studies have reported significant therapeutic efficacy in various types of cancers when combined with chemotherapy [14]. This combination prolongs Progression Free Survival (PFS) of patients with metastatic colorectal, lung, breast and kidney cancers [7–9,15]. Inhibitors of VEGF not only stop angiogenesis and destroy part of the tumor vasculature but they may play a role in the "normalization" of the tumor vasculature and improve drug delivery by the normalization of tumor blood vessels. This may explain the efficacy of combination of BVZ and chemotherapy [16] (Fig. 1).

1.1.2. Direct inhibition of the tyrosine kinase activity of receptors of angiogenic factors

Other anti-angiogenesis treatments target directly the kinase domain of receptors that bind angiogenic factors. Therapies that inhibit the activity of these receptors, mainly Receptors with a Tyrosine Kinase (RTK) activity, are called Tyrosine Kinase Inhibitors (TKIs). TKIs are small molecules that readily diffuse through the cell membrane to compete for ATP binding to the intracellular tyrosine kinase domain of the receptor, which results in the inhibition of downstream signaling pathways. A number of anti-angiogenesis drugs targeting RTK have been developed. Some of the most clinically relevant inhibitors include sunitinib (Sutent; Pfizer), pazopanib (Votrient; GSK), sorafenib (Bay 43-9006; Nexavar), vandetanib (Caprelsa; Astrazeneca), cabozantinib (XL184; Exelixis) and most recently axitinib (AG013736; Inlyta), tivozatinib (AV-951) and linifanib (ABT-869). Although they share the same mechanism of action, namely competitive ATP inhibition at the catalytic binding site of kinases, they differ in their spectrum of targeted kinases, their pharmacokinetics and their substance-specific adverse effects. For example, the two major small-molecule tyrosine kinase inhibitors sorafenib and sunitinib target the VEGF receptors (VEGFR), primarily VEGFR-2 but also block signaling by RAF, FLT3, PDGFRB, and KIT [17] and signaling by VEGFR1-3, FLT3, RET, PDGFRA, PDGFRB and KIT, respectively [18].

Sorafenib has been approved for un-resectable hepato-cellular carcinoma and advanced RCC. Results from phase III trials have shown significant benefit in patients with advanced hepato-cellular carcinoma and a more moderate effect in RCC when treated with sorafenib as monotherapy [19,20]. In RCC the benefit did not

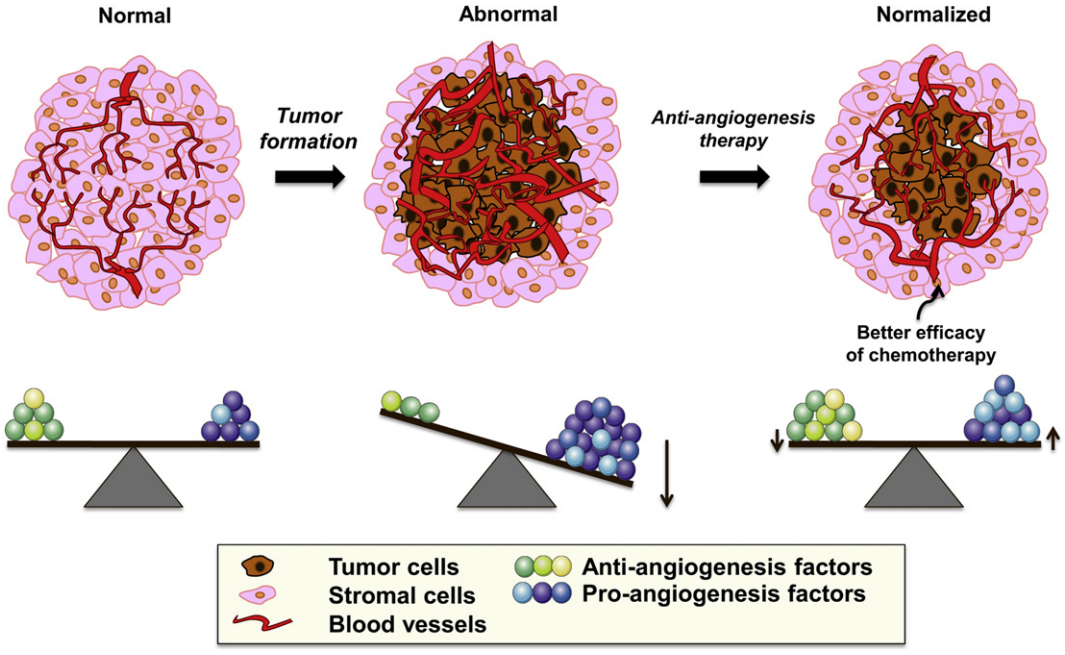

Fig. 1. Model of vessel normalization in tumor cells in response to anti-angiogenesis therapy. In normal tissues, the action of pro-angiogenesis factors is counterbalanced by the action of anti-angiogenesis factors. This balance is deregulated under pathological conditions particularly due to an increase in pro-angiogenesis factors, which is the case for tumors with a very abnormal vasculature. After anti-angiogenesis therapy a change in the balance of anti- and pro-angiogenesis factors in the tissue remodels vessels and vasculature "normalization" is observed. This more normal state improves delivery of chemotherapeutic agents [16].