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Review

Vaccination approach to anti-angiogenic treatment of cancer

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ABSTRACT

Improvement of patient survival by anti-angiogenic therapy has proven limited. A vaccination approach inducing an immune response against the tumor vasculature combines the benefits of immunotherapy and anti-angiogenesis, and may overcome the limitations of current anti-angiogenic drugs. Strategies to use whole endothelial cell vaccines and DNA- or protein vaccines against key players in the VEGF signaling axis, as well as specific markers of tumor endothelial cells, have been tested in preclinical studies. Current clinical trials are now testing the promise of this specific anti-cancer vaccination approach. This review will highlight the state-of-the-art in this exciting field of cancer research.

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1. Introduction

Angiogenesis is intricately regulated by a balance of many different endogenous activators and inhibitors. While a plethora of pro-angiogenic growth factors has been described, among which vascular endothelial cell growth factors (VEGFs) and fibroblast growth factors (FGFs) are the most prominent, a growing family of anti-angiogeneic molecules is also emerging [9,39]. Among the latter are molecules such as certain alpha-chemokines [124], interferon-alpha [127], tissue inhibitors of metalloproteinases [113], bactericidal permeability increasing protein [123], and breakdown products of angiogenic factors such as endostatin [88], tumstatin [43], and the 16k-fragment of prolactin [114]. Since new blood vessel formation is a critical step in the progression of cancer as well as in metastasis formation and outgrowth, it has been realized that inhibition of angiogenesis may be a tool to control cancer. The field of angiogenesis research has expanded explosively since its nativity, mainly after (pre)clinical validation of the concept in the early 1990s. The impact of the field increased with the understanding that also other angiogenic diseases may benefit, such as rheumatoid arthritis [119], inflammatory bowel disease [107] and age-related macular degeneration [104].

Inhibition of angiogenesis as a therapeutic approach was mostly developed in the oncological arena. Over the last decade, this research has led to the FDA approval of several angiogenesis inhibitors, the first one being bevacizumab (Avastin) in 2004. In combination with chemotherapy this drug has shown a clinical benefit for several indications, including metastatic colorectal cancer (mCRC) [52], metastatic renal cell cancer (mRCC) [21] and metastatic non-small cell lung cancer (mNSCLC) [106]. Several other targeted compounds with anti-angiogenic effects received FDA approval in the anti-cancer field in the years thereafter. Among these are aflibercept; a fusion protein binding VEGF; and the small-molecule tyrosine kinase inhibitors (TKI) sunitinib, sorafenib and pazopanib; which among other kinases bind VEGF receptors. Other anti-angiogenic compounds target mTOR. These compounds, e.g., everolimus, have a rather indirect activity and due to their blockade of key signal transduction molecules, may have a broader effect. The mTOR inhibitor everolimus exerts its anti-angiogenic effects by decreasing the levels of hypoxia inducible factor (HIF) and thereby the production of angiogenic growth factors by tumor cells. Moreover mTOR inhibition blocks the growth and proliferation of vascular endothelial cells [41]. However, although proof for the concept of tumoristatic activity of angiogenesis inhibition has been provided, the benefit of these anti-angiogenic agents on the progression-free survival and overall survival of cancer patients are still rather modest. The reason for this limited activity has been suggested to be due to variation among patients as well as in tumors, resistance mechanisms [33], the induction of a more aggressive tumor phenotype [98] and dose-limiting toxicities necessitating discontinuous treatments. In addition, an apparent discrepancy between clinical and preclinical in vivo dependence on angiogenesis for tumor growth and metastasis formation, makes translation of promising strategies to the clinic challenging [19].

It has been hypothesized that the limited success of anti-angiogenic treatment may also be due to the generally followed strategy of targeting tumor-derived growth factors and their receptors [35]. This strategy is likely to give growth advantage to mutated tumor cells that can rely on alternative growth factor pathways to attract blood vessels. Therefore, it has been suggested that a direct tumor endothelial cell targeting approach, in view of their genetic stability, should outperform most FDA approved drugs, and drugs currently in clinical testing. Consequently, genomic screening approaches to identify tumor endothelial cell markers are of key importance [121,4,110].

Over the last years it has become clear that tumor-infiltrating immune cells have important prognostic significance in cancer patients. This is in part regulated by angiogenic factors. Tumor infiltration with M2 macrophages [56], myeloid derived suppressor cells (MDSCs) [28], CD4+ T-helper2 (Th2) lymphocytes [12] and regulatory T cells (Treg) [11] is generally associated with a poor prognosis, whereas patients with tumors that are infiltrated by CD8+ T lymphocytes [20] as well as CD45RO+ memory T cells and Th1 lymphocytes [96,120], usually have a superior clinical outcome. Angiogenic growth factors that also contribute to the immunosuppressive tumor environment include VEGF, placental growth factor (PlGF) and transforming growth factor beta (TGF-β) [83,84]. This was reported in a series of papers in the mid-1990s showing that VEGF, secreted by tumor cells is able to inhibit the functional maturation of dendritic cells (DCs) [30]. These studies show that VEGF overexpression (i) impairs the antigen presenting cell (APC) function of DCs [13], (ii) can induce DCs to undergo apoptosis [116], (iii) inhibits effector T-cell development [89], (iv) increases the number of regulatory T cells in the tumor microenvironment [66], and (v) promotes the formation of tumor promoting MDSCs [29]. Also an indirect, endothelial cell mediated, immunosuppressive activity of pro-angiogenic factors was described, based on their suppression of endothelial adhesion molecules and subsequent suppression of leukocyte infiltration [37,38,78].

This immune suppressive activity of angiogenic growth factors urged researchers to investigate a presumed inflammatory activity of anti-angiogenic compounds. Indeed, there are indications that anti-angiogenic drugs are able to help reverse the immunosuppressive tumor microenvironment. Although the described effects of bevacizumab treatment on DC maturation are inconsistent [95,26,1,31], it seems that bevacizumab as well as sunitinib treatment reduces the number of immature myeloid cells and consequently MDSCs that can arise from them [95,26,61]. Furthermore, there is proof for the fact that treatment with low dose anti-angiogenic drugs polarizes tumor associated macrophages (TAMs) with an M2-skewed phenotype into an immunosupportive M1-like phenotype [50]. Other proposed mechanisms by which anti-angiogenic drugs can promote an immunosupportive tumor microenvironment include the increase of cell adhesion molecules (CAM), which promote leukocyte–endothelium interactions [15,16,14] and the reduction of regulatory T cell numbers [66].

Recent work demonstrated that a high baseline VEGF concentration correlates with poor outcome in metastatic melanoma patients treated with the immune checkpoint inhibitor ipilimumab [137]. Moreover treatment with ipilimumab or the GVAX vaccine can induce antibody responses against different pro-angiogenic players, including VEGF and angiopoeitin 1/2 [108]. This suggests that combining anti-angiogenic drugs with immunotherapy is worthwhile to investigate. Pre-clinical studies have shown enhanced effects of immunotherapy when combined with anti-angiogenic drugs [50,112]. Based on these results clinical trials have been initiated to investigate the potential synergy of this combination treatment. Recently the first clinical trial investigating the combination of ipilimumab and bevacizumab in patients with metastatic melanoma was published [46]. In one patient a complete response was achieved, eight patients had a partial response and 22 of the 46 treated patients showed stable disease. Immunohistochemical stainings showed enhanced immune cell infiltration after this combination therapy, as compared to ipilimumab monotherapy [46]. Whether the combination treatment is superior over ipilimumab monotherapy in terms of clinical outcome remains to be assessed in further studies.

The intricate relationship between the immune system and angiogenesis suggests a benefit of developing an immunotherapeutic strategy against angiogenesis. A vaccination approach against the tumor vasculature combines this benefit with enhanced selectivity against specific tumor endothelial markers. An additional advantage may be the possibility to circumvent the disadvantages of current anti-angiogenic compounds. To date, several studies have reported on the efficacy of this promising approach. This review will discuss these studies and will also highlight the results of recent clinical trials investigating this novel treatment strategy. We will end with an outlook on future directions to further this field.