Anti-Angiogenic Agents and Cancer: Current Insights and Future Perspectives

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Abstract: For sustained growth, tumors are dependent upon neovascularization to feed their massive demand for nutrients and oxygen. Cancer cells produce growth factors and activators that stimulate vessels in the surrounding tissue to form a new circulatory network around the tumor. Therapies aimed at reducing the blood flow to the cancer cells can slow down tumor growth and reduce metastasis. This review describes novel anti-angiogenic agents, including antibodies directed against vascular growth factors and angiotensin II, pharmaceutical compounds and natural metabolites derived from plants and microorganisms. The relevant patents are discussed. These agents may become valuable anti-cancer therapeutics in the future, as a supplement to chemo- and radiation-therapy.

Keywords: Angiogenesis, antibiotics, antibody therapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor 1 antagonists, combination therapy, matrix metalloproteinases, opioids, polyphenols, simmondsins, vascular endothelial growth factor inhibitors.

INTRODUCTION

The process of angiogenesis is regulated by both activator and inhibitor molecules. In adult tissues blood vessels are quiescent structures, and the inhibitors of angiogenesis predominate. When the need arises for neovascularization, the balance tips over to the activators, which prompts vascular endothelial cells to divide and form new blood vessels. This occurs only in specific physiological processes such as wound healing and during the menstrual cycle. Angiogenesis is a multi-step process tightly regulated through a myriad of cellular factors. The cascade of angiogenesis is initiated by the release of pro-angiogenic mediators that bind and activate endothelial cells. Through subsequent enzyme production, the basement membrane is degraded and the extra-cellular matrix (ECM) is remodeled, permitting endothelial cells to divide and migrate to the surrounding tissues. Endothelial cells are then positioned by means of adhesion molecules or integrins, allowing their organization into tubular structures and the formation of functional blood vessels.

In cancerous tissues, angiogenesis is promoted. To accommodate their growth, solid tumors release signal molecules to the surrounding host tissue that encourage the formation of new blood vessels. The newly formed network of blood vessels penetrates the cancerous growth, supplying the tumor with nutrients and oxygen, and removing waste products. Continuous neovascularization is a requisite for sustained tumor growth and metastasis. Taking this into account, anti-angiogenic therapy is an amenable approach for anti-cancer treatment.

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TARGETING ANGIOGENESIS

Endothelial Growth Factors

Tumor growth requires the continuous maintenance and expansion of its vascular network, which relies on the influx of endothelial cells. Activating endothelial cells is accomplished when the inhibiting factors that dominate under normal physiological conditions are overruled by stimulating factors. Tumor cells create such a pro-angiogenic micro-environment by producing endothelial growth factors. Vascular endothelial growth factor (VEGF) appears to be of primordial importance for sustained tumor growth, making it a potential target for anti-cancer therapy. Many pharmaceutical tyrosine kinase inhibitors have been developed that block signal transduction via VEGF receptors. The first compound tested was semoxinal, but anti-tumor response in renal and skin cancer was poor [1]. AZD2171 is an orally bioavailable growth factor receptor-2 tyrosine kinase inhibitor with potent anti-cancer activity [2]. Results of a phase I clinical study in patients with advanced solid tumors refractory or unsuited to standard treatment were encouraging, and demonstrated a dose-related control of tumor growth [3]. Sunitinib is a multitargeted tyrosine kinase inhibitor, which is efficient and safe in patients with advanced gastrointestinal stromal tumors after failure of imotinib [4]. Sorafenib (nexavar®, Bayer) is a small molecular inhibitor of several protein kinases including VEGF-receptors that has been FDA approved for the treatment of renal and liver cancers in 2005. Vatalanib is another potent oral tyrosine kinase inhibitor, but in a clinical trial this compound did not meet the primary objectives [5]. In comparison to these multi-targeted tyrosine kinase inhibitors, VEGF receptor blocking antibodies could be a more selective alternative [6]. The anti-VEGF antibody bevacizumab (avastin™, Genentech) has been shown to delay tumor growth and extend the life of cancer patients [7]. Based on a Phase III clinical trial

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that showed benefit in first-line treatment of metastatic colorectal cancer when added to standard chemo-therapy [8], avastin™ was FDA approved.

Another approach is to administer angiostatic factors as therapeutics. For this purpose, endogenous factors such as endostatin, angiostatin and interferons, or pharmaceuticals such as combretastatinA4 (Oxigene) could be administered. However, the question remains if this approach shows enough promise to be further explored, after what was rightly called 'the unfulfilled promise of endostatin' in a report describing results from a gene-therapy model [9]. Pigment epithelium-derived factor (PEDF) inhibits migration of endothelial cells specifically and is more potent than angiostatin [10]. This compound may be an alternative option to be explored in clinical trials [11].

ECM Breakdown and Adhesion

The breakdown of ECM is an essential event to facilitate endothelial cell migration, and matrix metalloproteinases (MMP) are key enzymes in these processes. MMP are produced as inactive pro-enzymes and are activated when necessary by cleavage of the amino terminal domain. The activated MMP are regulated individually by endogenous inhibitors among which the tissue inhibitors of MMP (TIMP). TIMP2 for instance, has been described as a specific MMP2 inhibitor [12]. Endogenous MMP inhibitors often have multiple anti-angiogenic properties, and TIMP3 has been shown to be a direct antagonist of the VEGF receptor [13]. Neovastat is a shark cartilage extract that contains the biologically active AE-941 molecule with strong anti-angiogenic activity, which appears also to act through multiple targets. AE-941 strongly inhibits the gelatinolytic and elastinolytic activity of MMP2, inhibits VEGF binding to its receptor [14], and induces apoptosis of endothelial cells [15]. Cartilage is a rich source of natural inhibitors of angiogenesis, as it is a site of poor blood supply that does not undergo neovascularization. Unfortunately, many naturally occurring MMP inhibitors have a poor oral bioavailability. Therefore, synthetic inhibitors are being developed better suited for clinical purposes. Batimastat, marimistat (both by British Biotech), CGS27023A (Novartis), prinomastat (Agouron), tanomastat (Bayer) and BMS-275291 (Bristol Myers Squibb) are competitive inhibitors that bind reversibly to the active site of MMP [16]. Although these synthetic MMP inhibitors worked well in animal models, results of clinical trials in cancer patients have been mostly disappointing [17].

Integrins are cell surface adhesion molecules that promote cell-cell or cell-matrix interactions. They mediate cell attachment to ECM proteins and to the intracellular cytoskeleton. Tumor cells often display upregulated integrin expression, which has been correlated with their ability to metastasize [18]. Integrin inhibitors could thus be of therapeutic use for their anti-angiogenic activity, as well as for preventing the spread of cancer cells to other tissues. Functional $\alpha5\beta1$-integrin is an essential requisite for the adherence of endothelial cells to the extracellular fibronectin network. When this interaction is blocked, migration of endothelial cells and the subsequent formation of new blood vessels is hampered [19]. The monoclonal anti-$\alpha5\beta1$-integrin antibody volociximab (PDL BioPharma and Biogen Idec) has entered Phase II clinical trials in cancer patients. The therapeutic use of chimeric and humanized $\alpha5\beta1$ integrin antibodies is currently being further explored [20]. In addition, several anti-$\alpha2\beta1$-integrin antibodies have become commercially available that may also be suited as anti-tumor agents [21].

The Renin-Angiotensin System

The renin-angiotensin system has a fundamental role in controlled vasoconstriction and blood pressure regulation. Through the action of renin, Angiotensin I is generated from angiotensinogen, which is later converted to active angiotensin II (AngII) by the angiotensin-converting enzyme (ACE). An alternative AngII-generating pathway exists in which other enzymes, such as chymase, are involved [22]. AngII positively regulates endothelial cell migration [23] and angiogenesis, the latter via upregulation of VEGF [24]. AngII acts through at least two high-affinity G-protein coupled receptors: AngII receptor 1 (ATR1) and 2 (ATR2). Most of the vascular effects of AngII, such as vasoconstriction and growth, are mediated via ATR1. Evidence implicating ATR1 signaling in the neovascularization, proliferation and invasion of tumors is compelling [25].

Angiotensin II Receptor Antagonists

ATR1 is the dominant receptor involved in various aspects of cancer progression [26], and many studies have become available that provide evidence of the involvement of ATR1 in breast cancer in particular [27]. Our own studies have revealed differential ATR1 expression in the breast epithelium of controls and breast cancer patients [28]. The upregulation of ATR1 in hyperplastic acini, a precursor of malignity, might be an important stepping stone for the development of breast carcinoma Fig. (**1**). Selective pharmaceutical ATR1 antagonists have been in use to treat hypertension since the 1990s [29]. A long list of compounds have been developed that posses high affinity for ATR1: losartan, valsartan, irbesartan, eprosartan, telmisartan, candesartan and tranilast. The use of these compounds has been shown beneficial to patients with hormone-refractory prostate cancer [30]. The anti-cancer action of ATR1 blocking antibodies has been explored through *in vitro* and *in vivo* studies with breast cancer cells. R6313/G2, a recombinant short-chain variable fragment form of the monoclonal ATR1 antibody was found to be more effective in suppressing cell proliferation *in vitro* and tumor growth *in vivo* than the ATR1 antagonist losartan [31].

ACE Inhibitors

ACE inhibitors prescribed for hypertension or other cardiovascular and renal diseases may reduce the risk of cancer in users, most particularly the risk of developing breast cancer [32], but data of epidemiological studies have not been consistent on this point. Nevertheless, ACE inhibition does display remarkable tumor-suppressive effects in experimental models [33] and ACE polymorphisms have been linked to either increased [34] or decreased [35] breast cancer predisposition. High expression levels of ACE correlate significantly with tumor VEGF expression in pancreatic ductal adenocarcinoma [36]. Many compounds

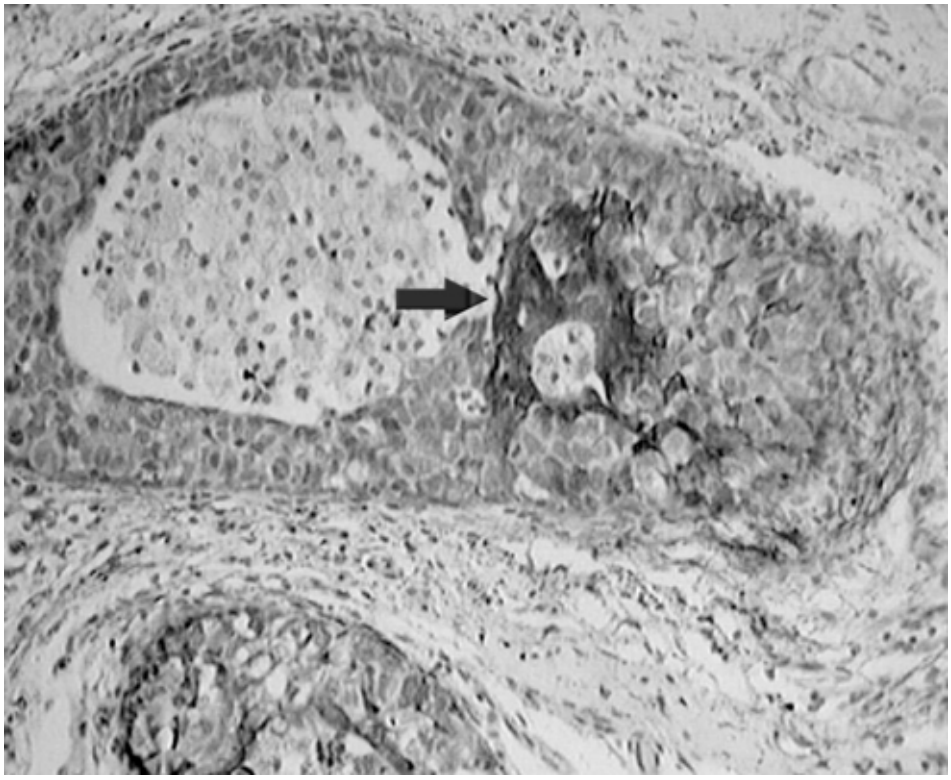

Fig. (1). Immunolocalization of Angiotensin II receptor 1 (ATR1) in ductal carcinoma *in situ* of the breast.
ATR1 was immunodetected with a polyclonal antibody as described in [28]. ATR1 is overexpressed on the membrane of luminal epithelial cells of ductal carcinoma *in situ* (arrow). Original magnification 400x.

exhibiting ACE inhibitory effects have been developed, and include quinapril, captopril, perindopril and enalapril. The inhibitory effect of captopril on tumor angiogenesis has been shown in an animal model more than a decade ago [37], and a Phase II randomized trial is ongoing in patients with lung cancer.

NOVEL TARGETS

Growth Factors and Receptors

Tumor cells are responsible for creating a pro-angiogenic micro-environment and produce signal molecules that stimulate endothelial cell growth and migration. Therapeutic approaches have currently focused on finding factors that reduce more selectively the activity and the migratory capacities of blood vessel endothelial cells. Such molecule-specific therapy necessitates a profound knowledge of the processes underlying tumor vascularization. Methods are proposed to identify and test therapeutic agents by providing nucleic acid sequences that mark an angiogenic disease [38]. This approach can generate important new information that could help to further unravel the complex interplay of tumor growth and angiogenesis. New anti-angiogenic factors are being put forward as possible therapeutics. Angiomotin controls endothelial cell migration [39] and angiomotin-like protein 1-derived molecules may have anti-angiogenic properties [40]. Somatostatin receptors are present in most hormone-producing tumors, and compounds that interact with somatostatin receptors may reduce tumor neovascularization [41]. The most potent anti-angiogenic effect was observed in compounds that interact with the somatostatin 5 receptor subtype.

The most common therapeutic use of antibodies is to administer blocking antibodies that deactivate angiogenic receptors. The novel thought of using antibodies that instead specifically bind and activate angiostatic receptors is offered in [42]. The target they put forward is CD148, an endothelial cell surface receptor protein tyrosine phosphatase that controls fundamental cellular processes, including growth and differentiation. Activation of CD148 has been shown to reduce angiogenesis [43]. CD148 signaling inhibits tumor cell growth and, not surprisingly, reduction of CD148 expression has been correlated with a malignant phenotype in breast cancer-derived cell lines [44].

Another novel target could be lanosterol 14α-demethylase, an enzyme essential for endothelial cell proliferation [45]. Inhibiting lanosterol 14α-demethylase with the anti-fungal drug itraconazole (sporanox^{TM}, Janssen) could thus be an amenable anti-cancer strategy [46].

Transcription Factors

A molecular approach to reduce angiogenesis would be to block endothelial cell specific promoter activity. Transcription factors that specifically bind and activate angiogenic genes, are rapidly being identified. The pre-proendothelin-1 (PPE1) promoter is an endothelial cell specific sequence. Gene therapy with an adenovirus-based vector expressing a

chimeric death receptor under control of such an endothelium specific promoter, could specifically eliminate this cell type, and thus inhibit angiogenesis [47]. Polynucleotide sequences with endothelial cell specific promoter activity, in particular to the PPE1 promoter could be future anti-tumor agents [48]. Transcription factors that regulate angiogenesis-related gene expression offer interesting avenues for anti-cancer treatment. The trans-cription factor RB2/p130 downregulates VEGF expression [49] and is inversely correlated with tumor aggressiveness in liver cancer patients [50]. Adenoviral vectors expressing RB2/p130 kill cancer cells and tumor endothelial cells [51]. Another potential target is the transcription factor hypoxia-inducible factor-1 (HIF1), which induces VEGF gene transcription. Aberrant expression of HIF1α protein has been observed in many human tumors and their metastases, and is associated with neovascularization [52].

NATURAL COMPOUNDS & DERIVATIVES

The large spectrum of anti-angiogenic metabolites produced by microorganisms and plants continues to offer basis for the development of novel anti-cancer therapies. One of the best known success stories in cancer therapy is that of paclitaxel (taxol®). This plant alkaloid with anti-microtubule characteristics was originally prepared from the bark of the Western or pacific yew. It can now also be synthetized in large quantities and researchers are currently seeking to modify the drug further, to create and test even more effective and selective derivates [53]. The anti-cancer characteristics of phytochemicals in spices has been reviewed in [54]. Gingerol, a pungent compound of ginger, for instance inhibits VEGF-induced angiogenesis *in vitro* and *in vivo* [55] and inhibits metastasis of breast cancer cells through interference with MMP activity [56]. Jojoba seed-derived simmondsins, which were earlier reported to be non-toxic food intake and body weight reducers [57], are currently explored for their angiostatic properties [58]. The anti-angiogenic activities of simmondsin derivates have been shown in *in vitro* and *in vivo* angiogenesis assays [59]. Oral intake of simmondsins inihits *in vivo* neovascularization of matrigel chambers in mice Fig. (**2**). Morphine, an opioid derivative originally extracted from poppies, has been shown to stimulate microvascular endothelial cell proliferation and angiogenesis. The use of opioid antagonists as anti-cancer agents has been put forward [60], and could be explored further [61]. From the non-oxidized, non-fermented leaves of Camellia sinensis, green tea is prepared of which consumption has been linked to reduced cancer risk [62]. Green tea polyphenols inhibit angiogenesis and metastasis, and epigallocatechin-3-gallate in particular reduces VEGF and MMP expression in human cancer cell lines [63, 64], and inhibits angiogenesis *in vitro* [65]. In line with these findings, substituted phenols are potential inhibitors of VEGF expression [66].

Several antibiotics have also been shown to exhibit anti-angiogenic properties. The diketodithiopiperazines for instance, secondary metabolites of moulds of the chaetomium strain, that include chaetocin, chaetomin and gliotoxin [67], are potential anti-cancer agents [68]. They interfere with the binding of HIF1α to its co-activator p300 [69] and

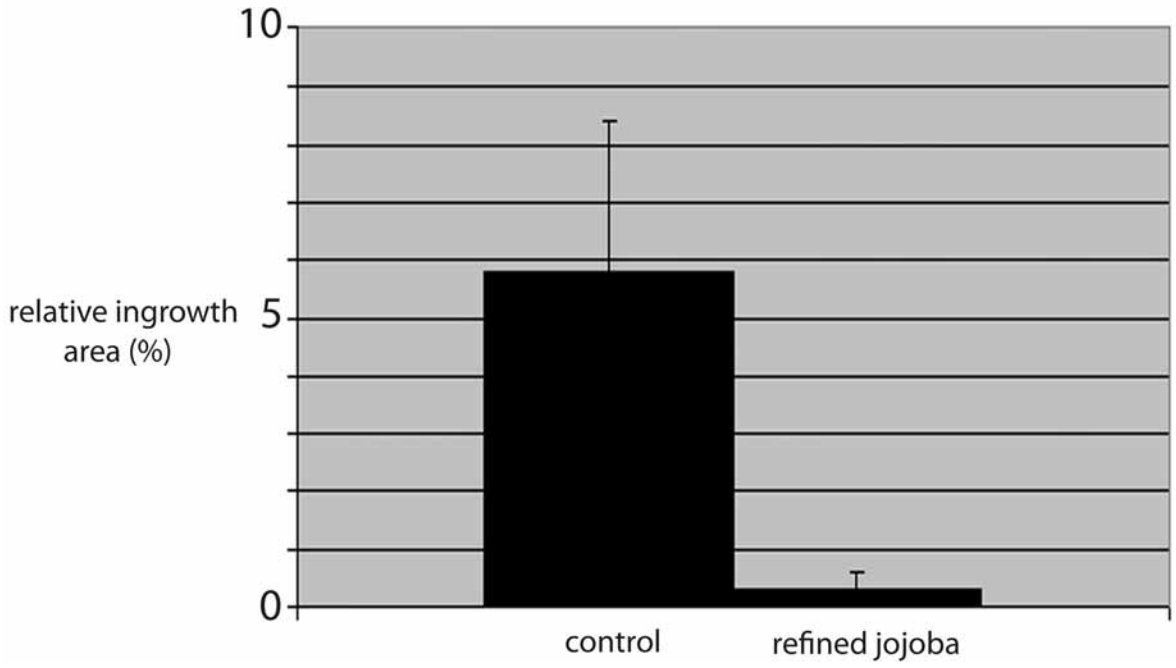

Fig. (2). Effect of simmondsins on basic fibroblast growth factor (bFGF)-induced vascularization of matrigel chambers *in vivo*.
Three FVB/N mice of 3 months old were fed ad libitum with Crispy rat food supplemented with refined, de-oiled jojoba flour at 2.7% w/w. Three mice were included as controls. The *in vivo* matrigel chamber assay was performed as described [59]. Filter chambers were fitted with a nylon membrane of 30μm pore sizes, injected with 100μl growth factor-reduced, phenol-red free matrigel and 200ng bFGF. Chambers were implanted subcutaneously into each mouse flank and scored with image analysis on day 14 post-implantation. The relative in growth area is given as mean ± range of two chambers, as percentage of the total matrigel area.

so reduce VEGF expression. Mithramycin is an aureolic acid-type polyketide and metabolite of Streptomyces bacteria that inhibits endothelial cell proliferation [70]. Reduced tumor growth and vascularization has been observed in human pancreatic cancer cells co-injected with mithramycin in the peritoneum of mice [71].

CURRENT & FUTURE DEVELOPMENTS

Cancer remains one of the top health threats, and there is a continuous and urgent need for more effective and more specific therapies. In this regard, anti-angiogenic agents may gain importance within the therapeutic arsenal available. However, many studies have reported minimal or no significant effects of anti-angiogenic agents on tumor progression. It is however anticipated that administering inhibitors of angiogenesis can potentiate tumor response to other therapeutic regimens, rendering the latter much more effective. In this respect, anti-angiogenic therapy can have a beneficial synergistic effect when used in combination with chemo-therapy. Clinical trials evaluating sorafenib in combination with various anti-cancer agents in different tumor types [72] have provided promising evidence that these combinations indeed increase the anti-proliferative and anti-angiogenic potential. Combination therapies using an anti-VEGF antibody and paclitaxel [73] or adding anti-VEGF antibody to a standard chemotherapy could increase the patient's response [6]. Combination therapies of an anti-VEGF antibody and anti-hypertensive agents such as ACE inhibitors, calcium-channel antagonists, AngII receptor antagonists, adrenergic receptor antagonists, vasodilators, and diuretic agents are suggested [74]. The patent states that combining VEGFR1R2-FcΔC1 with ACE-inhibitor or β-adrenergic receptor blocker works best to ameliorate cancer through regression or reduction of the size of the tumor.

In addition, anti-angiogenic therapy may also offers new routes in adjuvant therapy. Currently, postoperative adjuvant therapy to eliminate residual metastatic cancer cells mostly comprises chemotherapy, and presents with significant toxicities. More selective cytostatic agents including VEGF antagonists may have less undesired side effects [75]. Also, given before surgery, the angiostatic agents could improve the patient's systemic well being as well as reduce the tumor volume.

It can be concluded that the overwhelming evidence of neovascularization being an essential part of tumor progression and metastasis, warrants the continuous exploration of angiostatic therapy for cancer, and that research in this area remains of primordial importance for developing better therapies in the future.

CONFLICT OF INETREST

The author declares to have no conflict of interest.

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