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Review

Targeting Angiogenesis in Cancer Therapy

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Angiogenesis is an essential process in tumor growth. The concept of angiogenesis, when proposed by Folksman in 1971, had a great impact on cancer research and therapy, as the survival and proliferation of cancer depend on angiogenesis, which could be a target of cancer therapy. In subsequent decades, numerous antiangiogenic agents were developed, and some of them have been applied clinically. However, angiogenesis includes a complex and multistep process that has not been sufficiently elucidated. In this review, we focus on signaling pathways related with tumor angiogenesis and several antiangiogenic agents approved by the United States Food and Drug Administration or under investigation.

Key words: angiogenesis, cancer

Molecular targeted therapy has become a mainstay in cancer therapy, most often targeting small molecules expressed by cancer cells (*e.g.*, EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; BCR-ABL, breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 and Kit) that are closely related to carcinogenesis and drive the tumor growth. This strategy targets cancer cells themselves, and its use has resulted in a dramatic benefit in a certain subset of patients, though it has some critical problems, such as acquired resistance to molecular targeted agents, that indicate the difficulty of using the strategy to cure advanced cancer.

In recent years, the concept of a tumor's microenvironment associated with treatment sensitivity has gained attention. It has been known for a long time that tumors need abundant vessels for their growth. Folksman *et al.* presumed in 1971 that survival and proliferation of cancer depend on angiogenesis, which could be a target of cancer therapy [1]. According to them, tumors can initially grow by capturing oxygen and nutrition via diffusion from the surrounding microenvironment, but they cannot grow beyond 2 mm without angiogenesis [2]. Therefore, tumors secrete various pro-angiogenic factors for angiogenesis. In many aspects, tumor vessels are different from normal vessels. They are dilated, tortuous, and poorly covered with pericytes [3, 4]. This immature structure causes hyperpermeability of these vessels and elevated interstitial pressure resulting in insufficient blood flow, which might impair drug delivery to the tumors.

The term "angiogenesis" means the expansion of a vascular network by branching new vessels from existing ones, which is differentiated from "vasculogenesis," meaning de novo vascular formation at an avascular area chiefly in the embryonic stage. Angiogenesis is a complex physiological process. After the stimulus of various pro-angiogenic factors, including vascular

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endothelial growth factor (VEGF), which is described below, angiogenesis begins with the detachment of mural cells and local proteolysis of the vessel wall. Next, endothelial cells begin to proliferate and migrate, followed by sprouting and branching of new vessels. The endothelial cell at the front of the sprouting is called the "tip cell," and it is distinguished functionally and phenotypically from the endothelial cells existing at the lateral side, which are called "stalk cells." Finally, new vessels are maturated by covering mural cells.

In this manuscript, we first describe the major signaling pathways related to tumor angiogenesis, and we then describe the clinical application of targeting angiogenesis.

VEGF/Vascular Endothelial Growth Factor Receptor (VEGFR) (Fig. 1A)

VEGF-A. In 1983, Senger *et al.* discovered a small molecule inducing vascular leakage in a guinea-pig cell line and named it vascular permeability factor (VPF) [5]. Ferrara *et al.* isolated and cloned VEGF, which induces proliferation of endothelial cells, in 1989 [6]. Later, VEGF and VPF turned out to be the same molecule. VEGF has gene family members including VEGF-A, -B, -C, -D, and -E and placental growth factor (PlGF) [7]. Among them, VEGF-A has been the most characterized and is considered a key angiogenic factor with various splicing variants such as VEGF-A_{125}, -A_{145}, -A_{165}, -A_{183}, -A_{189}, and -A_{206} [8–10]. The term "VEGF" often refers to VEGF-A. VEGF-A is indispensable during embryonic vascular development, and even the loss of a single VEGF-A allele results in embryonic lethality with defective vasculature in a mouse model [11, 12]. Hypoxia, often seen in the center of tumors, strongly up-regulates VEGF-A expression via increased hypoxia inducible factor (HIF) [13]. Under normal conditions, HIF is ubiquitinated and degenerated by binding to von Hippel-Lindau (VHL) protein, but, in the hypoxic condition, HIF cannot bind to VHL, resulting in increased HIF. Increased HIF binds to the DNA chain at the HIF-1 binding site, the hypoxia response element (HRE), and enhances many pro-angiogenic gene transcriptional activities, including that of the VEGF-A gene [13].

VEGFR. VEGF family members bind to VEGFR (VEGFR-1, VEGFR-2, and VEGFR-3). VEGF-A binds to VEGFR-1 and VEGFR-2 [14]. Although the affinity of VEGF-A to VEGFR-1 is 10-fold higher than that to VEGFR-2, VEGF-A signaling is mainly mediated by VEGFR-2 because of its intense kinase activity [15, 16]. VEGFR-2 signaling in endothelial cells is mediated to downstream cascades such as PI3K/AKT, p38/MAPK, and PLCγ/MAPK, causing proliferation and migration of endothelial cells, production of proteases, and hyperpermeability of vessels [17, 18]. Currently, researchers agree that VEGF-A/VEGFR-2 signaling is the key pathway the mediates tumor angiogenesis.

VEGF-B and PlGF bind only to VEGFR-1, in contrast to VEGF-A, which binds to both VEGFR-1 and -2 [19]. VEGFR-1 signaling has more complex roles in angiogenesis compared with that of VEGFR-2. VEGFR-1 exists as a decoy receptor with high affinity to VEGF-A and little kinase activity preventing VEGF-A from binding to VEGFR-2 [14], so VEGFR-1 works as a negative regulator of angiogenesis. In fact, VEGFR-1 tyrosine kinase-deficient mice, with normal ligand binding ability and deficient signal transduction, developed normally [20], which means VEGFR-1 tyrosine kinase activity is not indispensable, at least during development. On the other hand, there is growing evidence that VEGFR-1 can mediate its ligand signals to downstream cascades. VEGFR-1 signaling in bone marrow cells such as macrophage lineage cells mobilized them to the tumor tissues, contributing to angiogenesis and tumor progression in a subcutaneous injected tumor model [21]. It has also been reported that VEGFR-1 signaling might be associated with metastasis [22, 23].

VEGFR-3 is reported to induce lymphangiogenesis after binding VEGF-C or -D [24, 25]. Lymphangiogenesis plays another important role in the tumor microenvironment and is considered the first step of tumor metastasis.

Angiopoietin/Tie2 (Fig. 1B)

Angiopoietin (Ang). Ang/Tie2 signaling is an endothelial cell-specific pathway, like VEGF/VEGFR signaling, but it is difficult to target for cancer therapy because of its complex system, as we will discuss later. Angiopoietins play an important role in vessel stabilization and maturation, though they cannot

directly induce tumor angiogenesis [26, 27]. Angiopoietins were identified in the 1990s. The human angiopoietin family includes three angiopoietins, Ang-1, Ang-2, and Ang-4 [28], all of which act as ligands for endothelial cell-specific tyrosine kinase receptor Tie2 [29–31]. To date, research has mainly focused on Ang-1 and -2.

Ang-1, expressed in many adult tissues, binds to Tie2 receptor as an agonist and causes Tie2 autophosphorylation, resulting in a facilitated connection between endothelial cells and mural cells [32]. Under physiological conditions, mural cells, including vascular smooth muscle cells and pericytes, constantly produce Ang-1 and maintain vascular stabilization and maturation. A recent study, however, reported a conflicting role of Ang-1, which was that Ang-1 promotes angiogenesis in some circumstance [33]. That is, Ang-1/Tie2 signaling promotes endothelial cell proliferation when endothelial cells are isolated, in contrast with promoting vessel stabilization when endothelial cells contact each other.

Ang-2, predominantly expressed in angiogenic vessels, acts as an antagonist for Tie2 by competing with Ang-1 [30], where it induces vascular destabilization and increased angiogenesis. But the role of Ang-2 seems to be altered by VEGF-A. In the presence of endogenous VEGF-A, Ang-2 increases tumor angiogenesis by promoting vessel destabilization, whereas Ang-2 promotes endothelial cell death and vessel regression in the absence of VEGF-A [34]. As noted above, angiopoietins play very complex roles in angiogenesis and antiangiogenesis.

Tie2. Tie1 and Tie2 receptors are endothelial cell-specific receptors expressed in vascular and lymphatic endothelial cells. There is no ligand identified for Tie1 receptor [28, 35]. Many tyrosine kinase receptors form dimerization during ligands binding, but Tie2 forms dimerization or multimerization on Ang-1/Ang-2 binding [36]. Although the Ang/Tie2 pathway has very complex roles, because agonistic and antagonistic ligands bind to the same receptor, blocking the Tie2 pathway in mouse models reduced tumor vascularization and growth [37, 38].

Platelet-derived Growth Factor (PDGF)/ Platelet-derived Growth Factor Receptor (PDGFR) (Fig. 1C)

PDGF. PDGF was first identified in 1974 [39]. Thus far, four PDGF family members have been identified, PDGF-A, -B, -C, and -D [40]. They form 5 kinds of homodimers and heterodimers, PDGF-AA, -AB, -BB, -CC, and -DD [40]. PDGFs generally act in a paracrine manner in a physiological condition or in epithelial cancers, whereas they act in an autocrine manner in gliomas, sarcomas, and leukemia [40]. PDGFs are secreted from various cells [40]. PDGF-A and -C are mainly secreted from epithelial cells, muscle, and neuronal progenitors. PDGF-B is secreted from vascular endothelial cells. PDGF-D secretion is not well understood.

PDGFR. PDGFs transmit their signal via PDGFRs. On binding PDGFs, PDGFR dimerizes, autophosphorylates at the tyrosine residues in the intracellular domain [41], and activates downstream pathways, including PI3K, Ras-MAPK, and PLCγ [40]. There are 2 types of PDGFRs, PDGFR-α and PDGFR-β [42]. PDGFRs can form 3 kinds of homodimers and heterodimers, PDGFR-$\alpha\alpha$, -$\beta\beta$, and $\alpha\beta$. Considering the five PDGF dimers described above, there could be multiple and complex PDGF/PDGFR pairings. To date, however, there are only three PDGF/PDGFR pairs proven to be functional *in vivo*, PDGF-AA/PDGFR-$\alpha\alpha$, PDGF-CC/PDGFR-$\alpha\alpha$, and PDGF-BB/ PDGFR-$\beta\beta$ [40]. PDGFR-α is involved in embryonic development, and PDGFR-β is involved in angiogenesis.

The PDGFR-α-induced pathway is involved in organogenesis such as alveogenesis, villus morphogenesis, hair morphogenesis, and oligodendrogenesis [40]. In addition, PDGFR-α might indirectly promote angiogenesis by recruiting stromal fibroblast-producing VEGF-A and other pro-angiogenic factors [43].

PDGFR-β signaling is involved in angiogenesis. PDGFR-β expression is found in pericytes but not in endothelial cells. Because of this, the PDGFR-β signaling pathway does not increase the tumor vessels themselves but maturates tumor vessels by recruiting PDGFR-β-expressing pericytes, accelerating tumor growth [44]. Blocking the PDGFR-β pathway inhibits matured vessels, eliciting detachment of pericytes

and disruption of tumor vessels, whereas blocking the VEGFR pathway impairs early-stage immature vessels lacking pericyte coverage but not large, well-covered vessels [45].

Delta-like Ligand 4 (DLL4) /Notch (Fig. 1D)

DLL4. If pro-angiogenic factors such as VEGFR-2 signaling stimulated all the endothelial cells, too much sprouting and branching would occur and the vascular structure itself would be destroyed. In fact, not all of the endothelial cells are stimulated, due to a mechanism deciding which endothelial cells should react to angiogenic stimulus and which should not. The DLL4/Notch pathway plays a key role in this mechanism.

DLL1, DLL3, DLL4, Jagged1, and Jagged2 bind to Notch receptor as ligands. Among these ligands, DLL4 has been the most intensely investigated in the area of tumor angiogenesis, because DLL4 is strongly expressed in tumor vascular endothelial cells but more weakly in normal vascular endothelial cells [46, 47]. DLL4 is a transmembrane ligand, and its expression in tumor vessels is regulated by VEGF-A. VEGF-A up-regulates DLL4 in the sprouting endothelial cells (tip cells), and up-regulated DLL4 interacts with Notch in the adjacent endothelial cells (stalk cells) [48, 49]. In reverse, the DLL4/Notch pathway down-regulates VEGFR-2 expression in Notch expressing endothelial cells, resulting in the reduction of VEGF-A-induced sprouting and branching [49]. Thus the DLL4/Notch pathway can be considered a negative feedback system of the VGFR pathway.

Notch. Notch receptors are single-pass transmembrane proteins in a family consisting of Notch1, Notch2, Notch3, and Notch4. The Notch receptor signaling pathway has a characteristic mechanism for transduction of its signaling [50]. After the ligand binding, Notch receptor is cleaved at the extracellular domain by proteases such as ADAM10 or TACE, followed by the cleavage at the transmembrane domain by γ-secretase. As a consequence, Notch intracellular domain translocates to the nucleus and activates the transcription of target genes.

Blocking the DLL4/Notch signaling pathway leads to increased angiogenesis, such as the enhancement of tip-cell formation, branching, and vessel density. Paradoxically, blockade of the DLL4/Notch signaling also leads to the inhibition of tumor growth in a variety of tumor models [47, 51, 52]. This is probably because increased tumor vessels induced by DLL4/Notch blockade are non-functional vessels resulting in tumor hypoxia [47].

Fibroblast Growth Factor (FGF)/ Fibroblast Growth Factor Receptor (FGFR) (Fig. 1E)

FGF1, FGF2. The FGF/FGFR signaling pathway plays an important role in embryonic organogenesis [53, 54], and disturbance of this pathway leads to various sorts of developmental defects [55, 56]. In the adult organism, FGF/FGFR signaling is involved in important physiological processes such as the regulation of wound healing and angiogenesis [57].

FGFs are heparin-binding growth factors that are part of a family that includes 23 members,; FGF1-23 [57]. Only 18 FGF members work as FGF ligands, because FGF11, 12, 13, and 14 are not functional ligands for FGFR, and the FGF15 gene does not exist in humans [57]. Among these family members, FGF1 and FGF2 are mostly described to possess a potent pro-angiogenic effect [58]. They induce the proliferation and migration of endothelial cells.

FGFR. FGFRs belong to a receptor family consisting of FGFR-1, -2, -3, and -4 [57]. FGFRs are expressed in most cells and have various functions, including normal cell growth, differentiation, and angiogenesis [59]. In many cancers, FGFR overexpression or mutation is found. FGFR activation has been shown to induce angiogenesis in a cell culture model and an animal model [59, 60].

Clinical Application of Targeting Angiogenesis

Currently, various antiangiogenic agents are in various stages of development. Among them, there are 5 agents clinically approved by the U.S. Food and Drug Administration (FDA), bevacizumab, sorfenib, sunitinib, pazopanib, and vandetanib. In this section, we will introduce these 5 agents and other antiangiogenic agents that are currently under investigation.

Bevacizumab (VEGF-A antibody). Bevacizumab was approved for clinical use as the first antiangiogenic molecular targeting agent. Bevacizumab is a

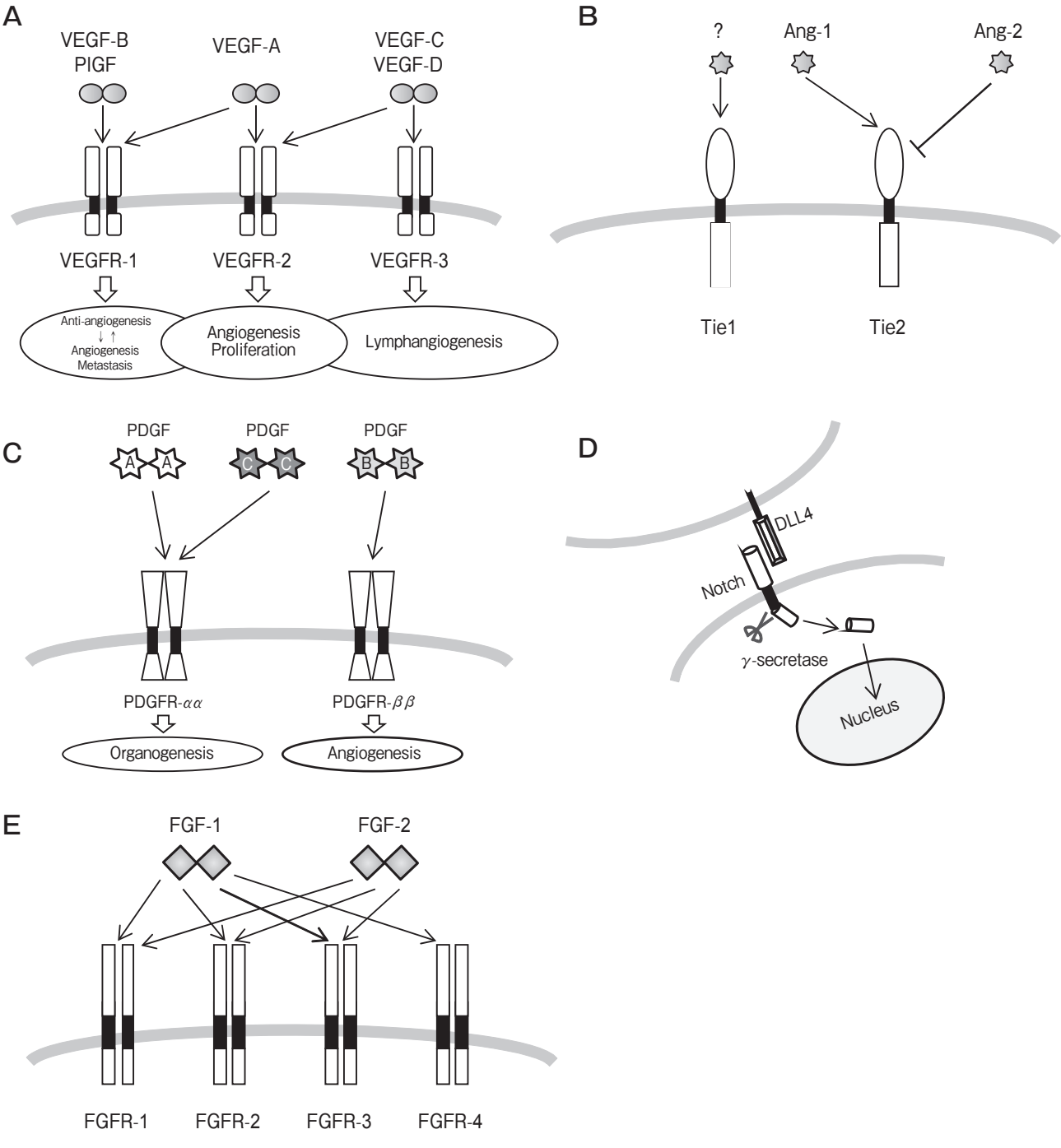

Fig. 1 Schema of receptors and their ligands. Each part of the figure represents the relation between a receptor and its ligands. **A**, Relation between VEGFR-1/-2/-3 and VEGF-A/-B/-C; **B**, Relation between Tie1/2 and Ang-1/2; **C**, Relation between PDGFRs and PDGFs; **D**, Relation between Notch and DLL4; **E**, Relation between FGFR-1/-2/-3/-4 and FGF-1/-2.

humanized monoclonal antibody against VEGF-A, preventing its binding to VEGFR. In examining the efficacy of anti-VEGF-A monoclonal antibody, it was initially reported that the antibody could inhibit subcutaneous tumor growth in a mouse model, despite its lack of efficacy in an *in vitro* model [61]. In clinical study, the efficacy of bevacizumab is mainly shown in combination with various cytotoxic agents; its efficacy as a single agent has not been proven [62]. The first phase 3 trial proving a survival benefit of bevacizumab was conducted in patients with advanced colorectal cancer [63]. This study compared irinotecan/ fluorouracil/leucovorin therapy (standard therapy at the time) with irinotecan/ fluorouracil /leucovorin plus bevacizumab. The addition of bevacizumab significantly improved overall survival (OS) by five months (15.6 months vs. 20.3 months, $p < 0.001$). In response to this result, the FDA approved bevacizumab for the treatment of advanced colorectal cancer. After that, favorable outcome in phase 3 trials was proved in various cancers, including renal cell cancer [64] and non-small cell lung cancer [65].

Aflibercept (VEGF-Trap). Aflibercept is another type of anti-VEGF-A agent. It has not yet been approved for clinical use. As stated previously, VEGFR-1 has higher affinity to VEGF-A than does VEGFR-2. Aflibercept utilizes the VEGFR-1 ligand-binding domain as a decoy (VEGF-Trap) and, at first, was synthesized by combining domain1-3 of VEGFR-1 and the Fc portion of immunoglobulin G1 (IgG1). But this agent was strongly charged positive and bound nonspecifically to negatively charged cell surfaces. Then, domain 2 of VEGFR-1, domain 3 of VEGFR-2, and the Fc portion of IgG1 were combined, and this improvement allowed aflibercept to possess high specificity to VEGF-A. It was confirmed in a xenograft model that aflibercept exerted an antitumor effect by inhibiting tumor angiogenesis [66]. Aflibercept is now being evaluated in various phase 3 studies including ovarian cancer, non-small cell lung cancer, colorectal cancer, and prostate cancer. In a phase 2 study of heavily pretreated advanced lung adenocarcinoma, 4 mg/kg of aflibercept showed minor single agent activity with 2.7 months of median progression-free survival (PFS) [67].

Sorafenib. Almost all small molecule antiangiogenic agents are multikinase inhibitors (Table 1), and many transmembrane receptors, including VEGFR, have similar kinase structures. Due to this multitargeting ability, small molecule antiangiogenic agents are not always regarded as a pure inhibitor of angiogenesis, and their efficacy might often be attributed not to their antiangiogenic effect but to their direct antitumor effect.

Sorafenib is the first small molecule antiangiogenic kinase inhibitor improved by the FDA, and it is now clinically used for advanced renal cell carcinoma and advanced hepatocellular carcinoma. Targets of sorafenb are VEGFR-2 and -3, PDGFR-β, RAF, and c-Kit. In a phase 3 study of advanced clear-cell renal-cell carcinoma, sorafenib reduced the risk of death as compared with a placebo (hazard ratio, 0.72; 95% CI, 0.54 to 0.94; $p = 0.02$) [68]. In a similar way, sorafenib prolonged OS by 2.8 months compared with a placebo for advanced hepatocellular carcinoma (hazard ratio, 0.69; 95% CI, 0.55 to 0.87; $p<0.001$) [69].

Sunitinib. Sunitinib is a multitargeting tyrosine kinase inhibitor against VEGFR-1, -2, and -3, PDGFR-β, c-Kit, and rearranged during transfection (RET) receptor. Sunitinib was approved for imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumors based on the data that sunitinib, compared with a placebo, significantly prolonged time

Table 1 Trargets of antiangiogenic agents and their developmental status

Agent	Targets	Developmental Status
Bevacizumab	VEGF-A	FDA approved
Aflibercept	VEGF-A	phase 3 study
Sorafenib	VEGFR-2, VEGFR-3, PDGFR-β, RAF, c-Kit	FDA approved
Sunitinib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, c-Kit, RET	FDA approved
Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, c-Kit	FDA approved
Vandetanib	VEGFR-2, EGFR, RET	FDA approved
Axitinib	VEGFR-1, VEGFR-2, VEGFR-3	phase 3 study
Cediranib	VEGFR-1, VEGFR-2, VEGFR-3	phase 3 study

to progression (hazard ratio, 0.33; 95% CI, 0.23 to 0.47; $p < 0.0001$) and OS (hazard ratio, 0.49; 95% CI, 0.29 to 0.83; $p = 0.007$) [70].

Sunitinib was next proved to be effective against metastatic advanced renal-cell carcinoma. PFS was significantly longer in the sunitinib group than in the interferon α group (11 months vs. 5 months, hazard ratio, 0.42; 95% CI, 0.32 to 0.54; $p < 0.001$) [71].

Pazopanib. Pazopanib targets VEGFR-1, -2, and -3, PDGFR-α and -β, and c-Kit [72]. In a phase 3 study, pazopanib demonstrated significant improvement in PFS and tumor response rate compared with a placebo in treatment-naive and cytokine-pretreated patients with advanced/metastatic renal cell carcinoma (9.2 months vs. 4.2 months, hazard ratio, 0.46; 95% CI, 0.34 to 0.62; $p < 0.001$) [73].

Vandetanib. Vandetanib inhibits VEGFR-2, EGFR, and RET receptor [62, 74]. This agent showed promising results against advanced non-small cell lung cancer in a phase 2 study [75] and was proved to be effective in a phase 3 trial in combination with docetaxel [76]. Its benefit was modest, however, and the application for FDA approval in non-small cell lung cancer was withdrawn. However, there recently is a growing awareness of the efficacy of blocking both VEGFR-2 and EGFR signaling [77, 78], because EGFR signaling might activate the VEGFR-2 pathway [79]. In the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, which selected a treatment modality depending on the character of the cancer biomarkers, lung cancer with expression of VEGFR-2 responded well to vandetanib which inhibits both VEGFR-2 and EGFR [80].

Vandetanib also showed benefits against medullary thyroid cancer and was approved by the FDA for the treatment of advanced medullary thyroid cancer.

Other antiangiogenic tyrosine kinase inhibitors. A great number of other antiangiogenic tyrosine kinase inhibitors are currently under investigation. Axitinib acts against VEGFR-1, -2, and -3 [81]. Recently, positive phase 3 trial results for axitinib in patients with previously treated metastatic renal cell carcinoma was reported, with axitinib significantly prolonging PFS compared with sorafenib (axis 1032 trial).

Cediranib is a VEGFR-2 inhibitor with additional inhibition effect against VEGFR-1 and -3 [82]. The addition of cediranib to carboplatin/paclitaxel improved PFS, but the toxicity was not acceptable at a 30-mg dose [83]. Currently a 20-mg dose of cediranib is being examined in the same trial design.

Problems of Antiangiogenic Therapy and Future Directions

Antiangiogenic therapy has achieved successful outcomes in several cancers in both basic and clinical study [61, 63, 72, 74, 77, 84–87], but this therapy is faced with emerging issues. One of them is the lack of a biomarker that predicts the efficacy of antiangiogenic therapy. Recently, biomarkers such as serum VEGF-A and microvessel density were reported as being predictive markers of antiangiogenic therapy [88, 89]. Many potent biomarkers must be validated, including those markers. Another issue is acquired resistance against antiangiogenic therapy. At first, antiangiogenic therapy was believed to rarely cause acquired resistance, because it targets not cancer cells themselves, which are genetically unstable, but genetically stable vascular endothelial cells. However, a recent study reported the emergence of acquired resistance to anti-VEGF therapy [90].

The era of antiangiogenic therapy has just begun. Most of the antiangiogenic agents have focused on the VEGF pathway. But now, many pathways related to tumor angiogenesis have been uncovered, and many agents have been developed that target these pathways. The role of antiangiogenesis will become more important in cancer therapy.

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