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Vascular endothelial growth factor pathway

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Description

Agents inhibiting tumor angiogenesis have been developed as a new class of anticancer agents (reviewed in Ref. [1]). Several of these therapeutics target the vascular endothelial growth factor (VEGF) signaling pathway (reviewed in Ref. [2]). VEGF comprises several isoforms which bind to different receptors, including FLT1, KDR, and NRP1, and promote angiogenesis through activation of a kinase cascade that includes RAS and MAPK. Drugs that are known to interfere with the normal VEGF signaling pathway include bevacizumab, a monoclonal antibody; sorafenib and sunitinib, small molecule kinase inhibitors; and experimental drugs aflibercept, brivanib, cilengitide, axitinib, motesanib, and vandetanib (Fig. 1).

Bevacizumab, a monoclonal antibody targeting *VEGFA*, is indicated in combination with intravenous 5-fluoruracil-based chemotherapy for first-line or second-line treatment of patients with metastatic carcinoma of the colon or rectum, and in combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous, nonsmall cell lung cancer. Bevacizumab is also indicated in combination with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and for glioblastoma, as a single agent for patients with progressive disease following prior therapy [Avastin (bevacizumab) drug label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf; retrieved 27 July 2009].

Sorafenib and sunitinib are small molecule kinase inhibitors [3–5]. They have overlapping activity but differing potency for inhibition of VEGFR1 (FLT1) and VEGFR2 (KDR), and sorafenib has high potency inhibition of Raf-1 (RAF1) and p38 MAP kinase (MAPK). Sunitinib has higher potency inhibition for kinases not depicted here. Sorafenib is indicated

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for the treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma [Nexavar (sorafenib) drug label: http://www.fda.gov/cder/foi/label/2007/021923s004s005s006s007lbl.pdf; retrieved 7 May 2009]. Sunitinib is indicated for the treatment of gastrointestinal stromal tumor after disease progression or intolerance to imatinib mesylate and for advanced renal cell carcinoma [Sutent (sunitinib) drug label: http://www.fda.gov/cder/foi/label/2007/021968s002s003s004s005s006lbl.pdf; retrieved May 7, 2009]. Brivanib, cilengitide, axitinib, motesanib, and vandetanib are experimental drugs influencing the angiogenesis pathway as depicted in Fig. 1 [6–11].

Recently, an association was found between *VEGFA* genotype and treatment outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab to treat metastatic breast cancer [12]. The AA genotype of VEGF: − 2578C > A (rs699947), a promoter polymorphism, was associated with superior median overall survival in patients receiving both paclitaxel and bevacizumab. Patients in the combination arm who carried the A allele of VEGF: − 1154G > A (rs1570360) also showed superior median overall survival. These results will require confirmation to support a role for *VEGFA* polymorphisms in affecting clinical outcome following bevacizumab treatment for metastatic breast cancer.

Several studies have investigated variants in angiogenesis pathway genes for association with disease risk. Studies focusing on *VEGFA* have produced conflicting results: Schneider *et al.* [13] reported that the A allele of *VEGFA*: − 2578C > A (rs1547651) and the C allele of *VEGFA*: − 1498T > C (rs833061) are associated with increased breast cancer risk. Lu *et al.* [14] found that the − 460C (rs833061) and +405G (rs2010963) *VEGFA* alleles were significantly associated with reduced overall survival after diagnosis of breast cancer, and that the − 460T/+405C/+936C (rs3025039) haplotype was significantly associated with increased overall survival. A large-scale evaluation of single nucleotide polymorphisms (SNPs) identified four SNPs in the *VEGFA* promoter region [the TT genotype of *VEGFA*:Ex1-73C > T (rs25648) the AA genotype of *VEGFA*: − 15648A > C (rs833052), the TT genotype of *VEGFA*: − 9228G > T (rs1109324), and the TT genotype of *VEGFA*: − 8339A > T (rs1547651)] that were associated with increased bladder cancer risk and one intronic SNP associated with reduced bladder cancer risk [the CT genotype of *VEGFA*:IVS2+1378C > T (rs3024994)] [15]. The CC genotype of *VEGFA*: − 1498T > C (rs833061) has been shown to be associated with decreased risk of bone metastases in breast cancer patients [16]. Other research has shown no association between *VEGFA* variants and risk of developing breast cancer [17–19], colorectal cancer [20], prostate cancer [21], or non-small cell lung cancer [22].

Selected polymorphisms in other VEGF pathway genes, including *KDR*, *FLT1*, *NOS3*, and *NRP1* were not associated with breast cancer risk [13]. The same study also found that the *NOS3*: − 786TT (rs2070744) genotype is significantly associated with greater likelihood of invasive breast cancer, and that the *NOS3*: 894GG (rs1799983) genotype is associated with increased likelihood of having metastatic disease. Further research is necessary to clarify the role of angiogenesis pathway gene variants in disease etiology and drug treatment outcome.

As a guide to future investigation of potential mechanisms of inter-individual variability of efficacy and toxicity, multiple signaling molecules and a simplified depiction of their interactions are diagrammed. While these signaling pathways are active in multiple cell types, the diagram and the supporting data are limited to the endothelial cell, as endothelial cells are thought to be the primary target of these agents in the treatment of cancer. Many more interactions and molecules have been described as important to angiogenesis and to VEGF signaling. This diagram, however, limits its scope to the molecules inhibited by the

depicted agents and the immediately interacting signaling molecules shown primarily in mammals or mammalian cell lines.

A clickable version of the VEGF pathway diagram and an Excel spreadsheet containing references for the pathway interactions depicted in Fig. 1 may be accessed at the Pharmacogenomics Knowledge Base (PharmGKB) at http://www.pharmgkb.org/do/serve?objId=PA2032&objCls=Pathway.

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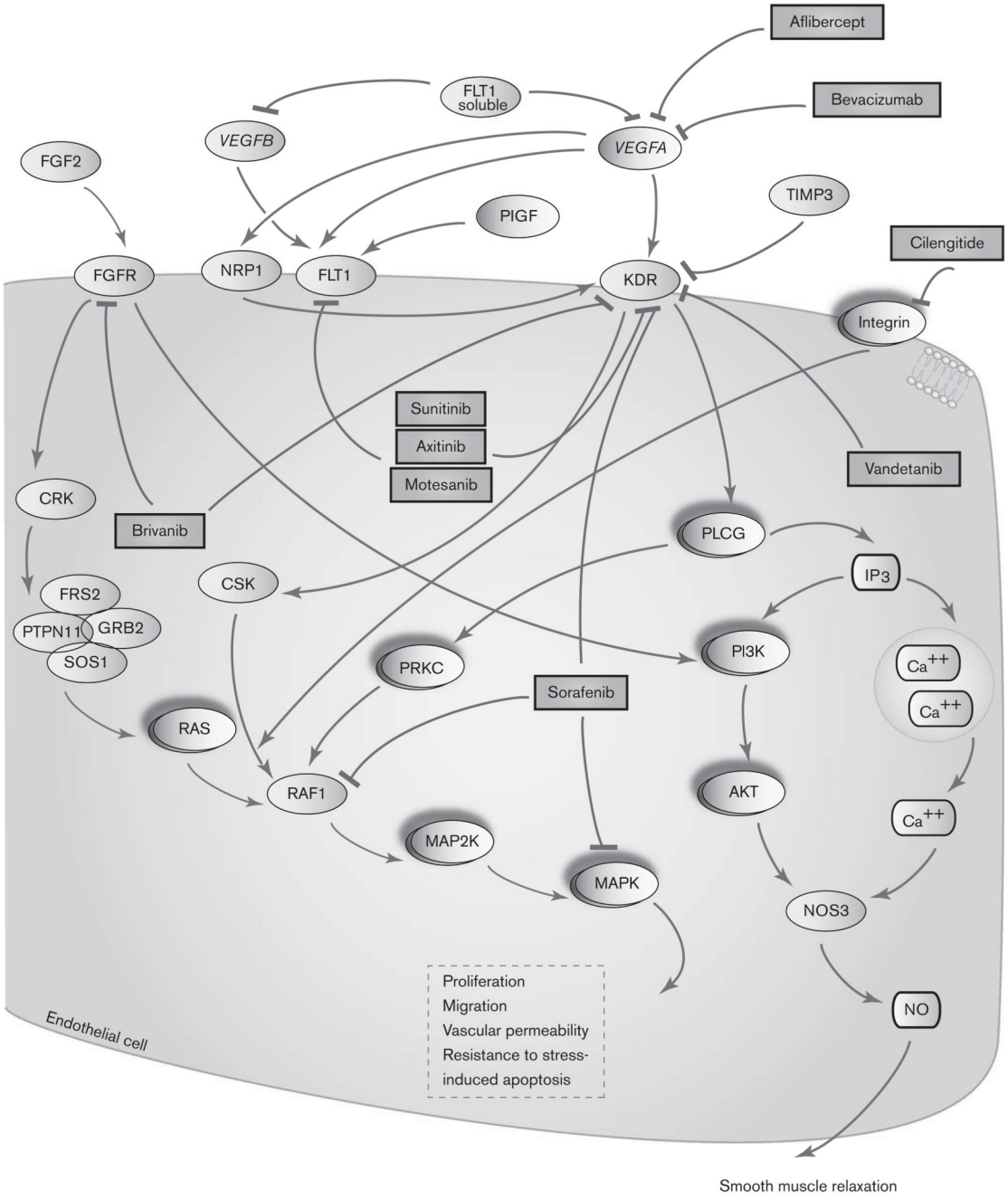

Fig. 1.

Representation of genes of the vascular endothelial growth factor (VEGF) signaling pathway and the sites at which bevacizumab, sorafenib, sunitinib, brivanib, and cilengitide are known to act.