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Commentary

Metabolic effects of antiangiogenic drugs in tumors: Therapeutic implications

Luigi Quintieri [a], Mohamed Selmy [b,1], Stefano Indraccolo [c,*]

[a] Dipartimento di Scienze del Farmaco, Università di Padova, Padova, Italy
[b] Medical Biochemistry Department, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
[c] Istituto Oncologico Veneto—IRCCS, Padova, Italy

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ABSTRACT

Antiangiogenic therapy has become a mainstay of cancer therapeutics, but clinical responses are generally short-term owing to the development of secondary resistance. Tumor starvation by antiangiogenic drugs is largely attributed to increased hypoxia and impaired nutrients supply, suggesting that angiogenesis inhibition causes remarkable metabolic perturbations in the tumor microenvironment. We review here recent acquisitions concerning metabolic effects of angiogenesis blockade in tumors and discuss the possibility that some metabolic features of tumor cells – i.e. their dependency from glucose as primary energy substrate – might affect tumor responses to anti-vascular endothelial growth factor treatment. Moreover, we discuss the hypothesis that anti-angiogenic therapy might foster metabolic evolution of tumors. The therapeutic implications of this hypothesis will be discussed further here.

1. Introduction

Angiogenesis is a tightly regulated biological process through which new blood vessels are generated from pre-existing ones. Following seminal observations by Folkman and other investigators in the 1970s [1], angiogenesis became a vivid area in cancer research and stimulated the search for conceptually new treatments. The identification of vascular endothelial growth factor (VEGF) as a key driver of the angiogenic process [2] has converted the VEGF/VEGF receptor (VEGFR) signaling pathway into an attractive therapeutic target. VEGF blockers belong to two broad categories including (I) VEGF ligand-blocking drugs and (II) drugs blocking VEGFR signaling. Not surprisingly, given the redundancy of factors involved in the regulation of the angiogenic process, also other angiogenic factors and signaling pathways – such as fibroblast growth factors (FGFs) and angiopoietins – have been considered as potential therapeutic targets [3,4]. After a decade of clinical research, we are currently at a critical point in the development of antiangiogenic drugs for cancer, as their therapeutic activity in patients has been substantially lower than expected based on preclinical findings. The development of assays to interrogate the dependence of individual tumors from any of these key angiogenic pathways will certainly be fundamental to personalize and possibly improve efficacy of antiangiogenic therapy.

Since the field of angiogenesis inhibitors is very large and the topic has been extensively reviewed elsewhere [5–7], we will briefly overview only a fraction of the antiangiogenic agents available, focusing on those in late stage clinical trials or approved by the regulatory agencies, being aware that more antiangiogenic drugs will enter the clinical arena in the coming years. A summary of the main characteristics and pharmacologic targets of these drugs is presented in Table 1, whereas their structure is shown in Fig. 1. Next, we will review literature linking antiangiogenic therapy to tumor metabolism, explain why we consider this an

* Corresponding author.
E-mail addresses: stefano.indraccolo@unipd.it, stefano.indraccolo@ioveneto.it (S. Indraccolo).
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Table 1
Antiangiogenic drugs approved for clinical use in cancer.

Drug	Target	Structure	Indications
Bevacizumab	All VEGF isoforms	mAb	mCRC [8], mRCC [8], NSCLC [9], rGBM [9], metastatic breast cancer [8] (EMA approval), advanced ovarian cancer [9] (EMA approval)
Sunitinib	VEGFR 1-3, c-Kit, PDGFR-α and -β, RET, CSF-1R, and FLT3	TKI	mRCC [10], GIST [11], PNET [12]
Sorafenib	VEGFR 2-3, PDGFR-β, FLT3, c-Kit, CRAF, BRAF, and P38-alpha	TKI	mRCC [15], advanced HCC [14]
Pazopanib	VEGFR 1-3, c-Kit, PDGFR-α and -β, FGFR-1 and-3, c-Kit, and c-Fms	TKI	mRCC [16], advanced ovarian cancer [17], soft tissue sarcoma [18]
Cediranib	VEGFR 1-3 and c-kit	TKI	mCRC [19], recurrent ovarian cancer [20]
Aflibercept	PIGF, VEGF-A, and VEGF-B	Fusion protein	mCRC [21]
Regorafenib	VEGFR 1-3, c-Kit, PDGFR-α and -β, FGFR 1-2, TIE2, RET, DDR2,RAF-1, and BRAF	TKI	mCRC [22], GIST [23]
Vandetanib	EGFR, VEGFR, RET, TIE2, and Src	TKI	Advanced medullary thyroid cancer[24]
Trebananib [AMG 386]	Ang-1/2	Peptibody	Recurrent ovarian cancer [17]
Brivanib	FGFR-1 and VEGFR-2	TKI	Advanced HCC [27]

c-Fms: transmembrane glycoprotein receptor tyrosine kinase, *c-kit:* stem cell factor receptor, *CSF-1R:* colony stimulating factor-1 receptor, *EGFR:* epidermal growth factor receptor, *FGFR:* fibroblast growth factor receptor, *FLT3:* fetal liver tyrosine kinase receptor-3, *GIST:* gastro-intestinal stromal tumor, *HCC:* hepatocellular carcinoma, *mCRC:* metastatic colorectal cancer, *mRCC:* metastatic renal cell carcinoma, *NSCLC*: Non-small cell lung cancer, *PDGFR:* platelet derived growth factor receptor, *PIGF:* placental growth factor, *PNET:* Pancreatic Neuro-ectodermal tumor, *RAF:* murine leukemia viral oncogene homolog, *RET:* rearranged during transfection, *rGBM:* recurrent glioblastoma, *Src:* v-src sarcoma viral oncogene homolog, *TIE2:* tyrosine kinase with immunoglobulin like and epidermal growth factor like domains 2, *VEGF:* vascular endothelial growth factor, *VEGFR:* vascular endothelial growth factor receptor, *mAb:* monoclonal antibody, *TKI:* small molecule tyrosine kinase inhibitor.

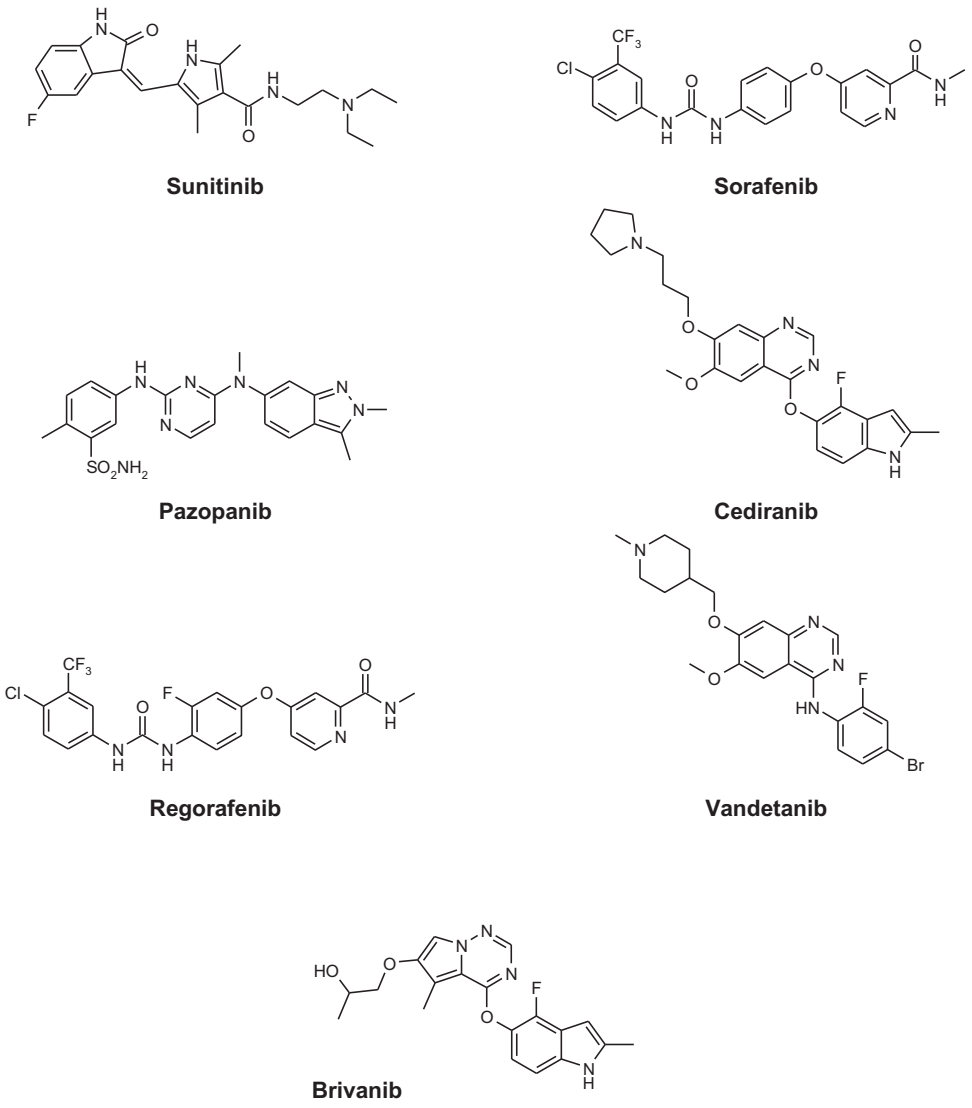

Fig. 1. Structures of small-molecule angiogenesis inhibitors listed in Table 1.