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Review

Angiogenesis inhibitors as therapeutic agents in cancer: Challenges and future directions

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ABSTRACT

Angiogenesis has become an attractive target for cancer therapy since the US Food and Drug Administration (FDA) approved the first angiogenesis inhibitor (bevacizumab) for the treatment of metastatic colorectal cancer in 2004. In following years, a large number of angiogenesis inhibitors have been discovered and developed, ranging from monoclonal antibodies, endogenous peptides, to small organic molecules and microRNAs. Many of them are now entering the clinical trial, or achieving approval for clinical use. However, major limitations have been observed about angiogenesis inhibitors by continued clinical investigations, such as resistance, enhancing tumor hypoxia and reducing delivery of chemotherapeutic agents, which might be the main reason for poor improvement in overall survival after angiogenesis inhibitor administration in clinic. Therefore, optimal anti-angiogenic therapy strategies become critical. The present review summarizes recent researches in angiogenesis inhibitors, and proposes a perspective on future directions in this field.

1. Introduction

Solid tumor, as a major type of cancer, is often treated with combination of surgery, chemotherapy, and/or radiation therapy. However, there are numerous challenges in classical chemotherapy, such as resistance and harmful side effects, resulting in the high cancer mortality (Torre et al., 2016). Therefore, new focuses in cancer treatment have been emerging in the past decade, including treatments based on histological subtypes and leveraging the tumor microenvironment (Singh et al., 2016). Another alternative target for tumor therapy as an adjunct to other forms of therapy is the vascular system, which is underscored by the fact that angiogenesis plays a pivotal role in the development, progression, invasion and metastasis of solid tumors (Hanahan and Weinberg, 2011).

Angiogenesis refers to the formation of new blood vessel from pre-existing vessels. It is a complex multistep process, and tightly regulated by a fine balance between inducers and inhibitors that act together to maintain physiological homeostasis (Hanahan and Folkman, 1996). However, proliferating tumor tends to activate angiogenesis by shifting the balance of inducers and inhibitors towards a pro-angiogenic outcome, to fulfill its increased demand of oxygen and nutrients (Carmeliet, 2005). Environmental hypoxia in tumor seems to be a primary factor that turns on 'angiogenic switch' by enhancing expression and activation of transcription factor hypoxia-inducible-factor-1 (HIF-1) pathway or HIF-1-independent pathways, and induces the expression of multiple genes contributing to the angiogenic process (Pugh et al., 2003). In 1972, Folkman proposed anti-angiogenesis as a new anticancer strategy for the first time (Folkman, 1972). Seventeen years later, the isolation and cloning of vascular endothelial growth factor A (VEGFA) became a landmark in understanding angiogenic mechanism (Keck et al., 1989), and laid a foundation for the novel field of research into anti-angiogenic treatments for cancer. The active research in this field eventually resulted in US Food and Drug Administration (FDA) approval of bevacizumab (a monoclonal antibody for VEGFA) as the first anti-angiogenic drug for colorectal cancer in 2004 (Hurwitz et al., 2004).

In the past ten years, many potential anti-angiogenic targets were discovered successively, including fibroblast growth factor, matrix metalloproteinase, tumor-associated stromal cell, and cell adhesion molecule (El-Kenawi et al., 2013). Among them, VEGFs and their receptors (VEGF receptor-1, VEGF receptor-2, and VEGF receptor-3), which are characterized by tyrosine kinase activity, play key roles in angiogenesis (Ferrara et al., 2003). Therefore, most of the angiogenesis inhibitors are developed targeting VEGFs or their receptors. To date, a large number of angiogenesis inhibitors have been discovered and developed, ranging from monoclonal antibodies, endogenous angiogenesis peptide inhibitors, to small molecule drugs and microRNAs (Blaschuk, 2012; Huang et al., 2010; Kim et al., 1993; Wang et al.,

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Table 1
Angiogenesis inhibitors and their indications in cancer patients.

Categories	Examples	Targets	Indications[a]	References
Protein inhibitors	Bevacizumab	VEGF-A	**Metastatic colon cancer, advanced nonsquamous non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), ovarian cancer, glioblastoma multiforme, advanced cervical cancer**	Hsu and Wakelee, 2009; Tewari et al., 2014
	Ramucirumab	VEGF receptor-2	**Advanced gastric or gastro-esophageal junction adenocarcinoma, NSCLC, advanced colorectal cancer**	Grabowski and Glode, 2016
	Cetuximab	EGF receptor	**Metastatic colon cancer, squamous cell carcinoma of head and neck**	Bokemeyer et al., 2012; Sotelo et al., 2014
	Ziv-aflibercept	VEGF receptor-1, VEGF receptor-2, Placenta growth factor (PIGF)	**Metastatic colorectal cancer**	Scartozzi et al., 2016
	Volociximab	Integrin α5β1	Advanced NSCLC (phase 1 clinical trial)	Besse et al., 2013
	IMC-18F1	VEGF receptor-1	Being tested in preclinical trial	Schwartz et al., 2010
Peptide inhibitors	ADH-1	N-cadherin	Advanced solid tumors which express N-cadherin (phase 1 clinical trial)	Yarom et al., 2013
	Endostatin	Multiple-pathways including C-Jun N terminal kinase (JNK), Integrin α5β1, VEGF receptor-2, et. al.	NSCLC (phase 1 clinical trial), recurrent nasopharyngeal carcinoma (approved in China)	Tang et al., 2016
	Rh-angiostatin	Multiple-targets including angiomotin, endothelial cell surface ATP synthase, integrins, annexin II	NSCLC (phase 2 clinical trial)	Redlitz et al., 1999
Small molecule inhibitors	Sunitinib	Multi-targets including VEGF receptors, PDGF receptors, CSF1 receptor, c-kit,	**RCC, imatinib-resistant gastrointestinal stromal tumor**	Gan et al., 2009
	Sorafenib	VEGF receptor-2, VEGF receptor-3, PDGF receptor-β, Flt-3, c-kit, Raf kinase	**hepatocellular carcinoma**, thyroid cancer and desmoids tumor (phase 3 clinical trial)	et al., 2009
	Vatalanib	VEGF receptors, EGF receptors, orphan receptor tyrosine kinase (RET)	Metastatic pancreatic cancer (phase 3 clinical trial)	Dragovich et al., 2014
	Axitinib	VEGF receptors, PDGF receptor, c-kit	**Advanced RCC**	Wang et al., 2016
	Pazopanib	Multiple targeted receptor TKI	**RCC, soft tissue sarcoma**	Kim et al., 2016
	Vandetanib	VEGF receptors, EGF receptors, RET	**Metastatic medullary thyroid cancer**	Thornton et al., 2012
	Nintedanib	VEGF receptors, FGF receptors, PDGF receptor	NSCLC (approved in European Union)	Popat et al., 2015

[a] "Indications" refers to FDA approved indications (highlighted in boldface) and any indication that was being tested (preclinical, phase 1, 2, or 3 clinical trial).

2013). This review summarizes recent researches in angiogenesis inhibitors, and proposes a perspective on future directions in this field.

2. Protein/peptide inhibitors

2.1. Protein inhibitors

Monoclonal antibodies targeting VEGF pathway have been used as a significant addition to cancer therapy. Bevacizumab (Avastin), a humanized monoclonal immunoglobulin G1 antibody, is the most widely studied anti-angiogenic agent across tumor types and settings, which prevents VEGFA from binding to receptors and activating signaling cascades that lead to angiogenesis (Ferrara et al., 2004). Bevacizumab received its first approval by FDA for combination use with standard chemotherapy for metastatic colon cancer, and then was approved for use in advanced nonsquamous non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), ovarian cancer, glioblastoma multiforme, and advanced cervical cancer after 2004 (Hsu and Wakelee, 2009; Tewari et al., 2014). However, not all tumor types received significant benefit from bevacizumab. For example, it had been approved for the treatment of metastatic human epidermal growth factor (EGF) receptor 2-negative breast cancer in combination with paclitaxel in 2008, nevertheless later studies failed to show a significant benefit in overall survival (OS) or quality of life, which resulted in the FDA withdrawing that approval in 2011 (Brufsky et al., 2011; Miller et al., 2007). Although there were some failures in clinical application, the use of bevacizumab as additional treatment in advanced cancer is still ongoing. Very recently, addition of bevacizumab to pemetrexed plus cisplatin for newly diagnosed pleural mesothelioma was studied in phase 3 trial (Zalcman et al., 2016). The results showed

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