Journal of Advanced Research 8 (2017) 591–605

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Review

Anti-angiogenic agents for the treatment of solid tumors: Potential pathways, therapy and current strategies – A review

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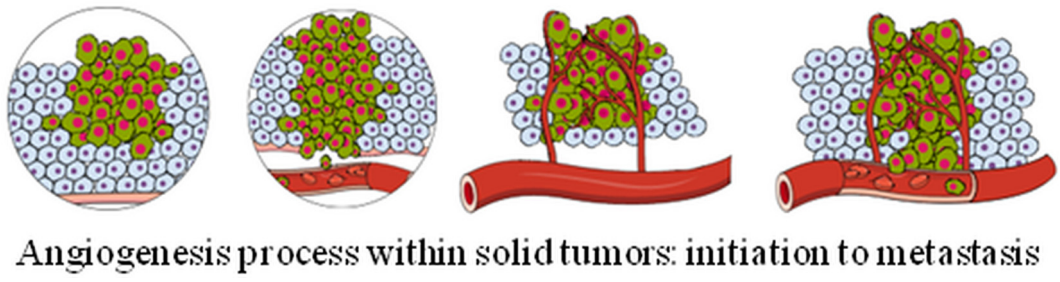
GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 2 March 2017
Revised 20 June 2017
Accepted 26 June 2017
Available online 27 June 2017

Keywords:
Angiogenesis inhibitors
Receptor protein-tyrosine kinase
Tumor microenvironment
Natural products

ABSTRACT

Recent strategies for the treatment of cancer, other than just tumor cell killing have been under intensive development, such as anti-angiogenic therapeutic approach. Angiogenesis inhibition is an important strategy for the treatment of solid tumors, which basically depends on cutting off the blood supply to tumor micro-regions, resulting in pan-hypoxia and pan-necrosis within solid tumor tissues. The differential activation of angiogenesis between normal and tumor tissues makes this process an attractive strategic target for anti-tumor drug discovery. The principles of anti-angiogenic treatment for solid tumors were originally proposed in 1972, and ever since, it has become a putative target for therapies directed against solid tumors. In the early twenty first century, the FDA approved anti-angiogenic drugs, such as bevacizumab and sorafenib for the treatment of several solid tumors. Over the past two decades, researches have continued to improve the performance of anti-angiogenic drugs, describe their drug interaction potential, and uncover possible reasons for potential treatment resistance. Herein, we present an update to the preclinical and clinical situations of anti-angiogenic agents and discuss the most recent trends in this field.

Peer review under responsibility of Cairo University.
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http://dx.doi.org/10.1016/j.jare.2017.06.006
2090-1232/

Introduction

Cancer is one of the leading causes of death and constitutes a national and international health problem regardless of the development status of the country (developed, developing or undeveloped country) [1]. Yet, no single outstanding anticancer treatment has been discovered. The World Health Organization (WHO) reported ideological failure in changing the mortality attributed to cancer over the past 5 decades (1950–2000), in contrast to other death-causing diseases [2]. Solid tumors constitute more than 94.4% and 96.8% of cancer-caused mortalities in males and females, respectively [3]. Recent strategies, other than just discovering novel anticancer agents, have been under intensive development such as pharmacokinetic utilization of the anti-angiogenic therapeutic approach [4]. Specifically, deregulation of angiogenesis by synthetic and natural products is being accepted as a good target for cancer prevention and treatment [5–8].

Angiogenesis phenomenon in healthy and diseased tissues

The term "angiogenesis" was introduced in 1787 by the British surgeon John Hunter in order to describe the formation of new vessels in the process of wound healing [9]. Angiogenesis is an essential, temporary physiological process of forming a new vascular tree from an existing one to supply a certain tissue with oxygen and nutrients as well as removing its carbon dioxide and waste products. Apart from embryogenesis, in rare cases, angiogenesis can be a healthy process such as during wound healing and the menstrual cycle [10]. Vasculogenesis is a different process in which blood vessels are formed from angioblast cells (rather than from mature blood vessels) during embryogenesis [11]. Prolonged angiogenesis is usually indicative of a pathological condition such as arthritis, diabetic retinopathy or cancer progression [12]. The differential activation of angiogenesis between normal and tumor cells makes this process an attractive strategic target for anti-tumor drug discovery. The principles of anti-angiogenic treatment were originally proposed by Judah Folkman in 1972, and ever since, the ability of a tumor to form new blood vessels to feed their abnormally high growth rate has become a therapeutic target. Hence, this has become a putative target for therapies directed against solid tumors [12–14].

Targeting tumor angiogenesis not only confers relative selectivity to tumor tissue but also enables the targeting of wide-range heterogeneous tumors that only share high angiogenic potential. Within the human body, angiogenesis is orchestrated by two sets of regulatory molecules with opposing functions; pro-angiogenic molecules (such as vascular endothelial growth factor, VEGF) and anti-angiogenic molecules (such as thrombospondin-1) [15]. Under homeostatic conditions, pro/anti angiogenic balance is shifted toward anti-angiogenic factors, resulting in quiescent blood vessels. On the other hand, the angiogenic balance in neoplastic lesions is shifted toward pro-angiogenesis [16]. This pathological transition is known as the angiogenic switch. Tumor hypoxia is believed to be the main pathological deriver behind this switch [17]. The release of pro-angiogenic factors from tumor cells and host cells, such as macrophages, causes disruption of the surrounding vasculature's basement membrane which is attributed to the activation of a group of proteases, such as plasminogen activator and collagenases [18]. These pro-angiogenic factors also work as chemotactic factors for endothelial cells (ECs), causing migration and proliferation within the tumor tissue and thus forming a vascular lumen structure [10]. In addition, the released angiogenic factors attract circulating bone marrow progenitor cells and stimulate their differentiation into ECs [19]. Then, new basement membrane is formed, and pericytes are attracted to circumvent the neo-vessel [20]. Apart from meeting the metabolic demands of the pre-existing tumor cells, these neo-vessels support further tumor growth and invasion [21]. In addition, intratumoral angiogenesis could serve as potential gateway to spread tumor cells toward distant tissues and facilitate the process of metastasis [22]. Interestingly, pathogenic induction of intratumoral angiogenesis appears to begin as early as during the pre-malignant phase of tumor development [23].

The degree of angiogenesis is not similar in all tumor types. Pancreatic neuroendocrine carcinoma is a highly vascularized tumor, while pancreatic ductal adenocarcinoma possesses low angiogenic potential [24,25]. In addition, the degree of vascularization varies from one micro-region to another within the same tumor tissue [26]. Sustained activation of angiogenesis within tumor micro-regions ultimately results in hypervascular structure with dysfunctional endothelium. These neo-vessels are characterized by increased permeability and leakiness [27]. In addition to ECs, pericytes are vascular support cells that functionally and structurally support the vascular endothelium. Yet, pericytes tend to be loose around intratumoral vasculature, suggesting a potential reason for the high permeability of tumor vasculature [28]. In 1989, the successful cloning of vascular endothelial growth factor-A (VEGF-A) could be considered the first clue to understanding the molecular bases of angiogenesis in solid tumors [29].

Principles of anti-angiogenic treatment for cancer "tumor under siege strategy"

Normal blood vessels are classified into three major types according to their endothelial lining and their underlying basement membranes. 1 – Continuous capillaries which are characterized by continuous sheets of sub-endothelial basement membrane and tightly packed monolayer of endothelium to prevent uncontrolled transfer of substances such as in blood brain barrier. 2 – Fenestrated capillaries which are characterized by continuous sheets of sub-endothelial basement membrane and loosely packed monolayer of endothelium to allow regular substances transfer (*e.g.* lung and GIT). 3 – Perforated capillaries which are characterized by perforated sheets of sub-endothelial basement membrane and loosely packed monolayer of endothelium to allow transfer of macromolecules such as hormones and peptides (*e.g.* endocrine glands). Intratumoral blood vessels are phenotypically similar to perforated capillaries; however, they are premature and possess unique peculiarities. In contrast to normal blood vessels, the intratumoral blood vessels are immature, highly permeable, and chaotic with heterogeneous and interrupted blood flow [30]. Angiogenesis inhibition is a potential novel appealing strategy for the treatment of solid tumors which basically depends on cutting off the blood supply to tumor micro-regions, resulting in pan-hypoxia and pan-necrosis within solid tumor tissues. Selectivity of anti-angiogenic agents toward intratumoral vasculature depends mainly on the phenotypic differences between the premature intratumoral vasculature and normal blood vessels. These phenotypic differences result in relative increased sensitivity of the intratumoral blood vessels to anti-angiogenic agents. The general mechanism of action of angiogenesis inhibitor (AI), nonetheless, vascular disrupting agent (VDA) is through induction of morphologic changes in the intratumoral endothelium; this in turn triggers a cascade of events that ultimately leads to vascular shutdown and tumor necrosis [30]. Initial events can be detected as early as 5–25 min following drug administration in the form of increased vascular permeability, vasoconstriction of tumor-supplying arterioles, reduction of blood flow and tumoral pan-hypoxia [31]. A few hours