Tumor angiogenesis and its current treatments: a short review

Dhamraa Waleed Ahmed

EMAN Research and Testing Laboratory, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia

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Significance | A cancer short review with angiogenesis

Graphical Abstract

*Correspondence: EMAN Research and Testing Laboratory, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia. E-mail: dhamora@yahoo.com

Tumor angiogenesis and its current treatments: a short review

Dhamraa Waleed Ahmed

Abstract

Angiogenesis is the process of formation new blood vessel. This process involves the migration, differentiation and growth of endothelial cells that line the inside wall of blood vessels (Folkman, 2007). Angiogenesis and inflammation, two host-dependent and interdependent hallmarks of cancer, play a critical role in the growth and spread of cancer. Tumors can stimulate angiogenesis by giving off chemical signals to increase blood flow to the tumor by promoting nearby normal cells to produce angiogenesis signaling molecules (Sturk, 2005). During critical tumor growth, the diffusion of nutrients and oxygen to the center of the tumor can become difficult, which causes a state of cellular hypoxia that marks the onset of tumoral angiogenesis. New blood vessel development during tumor progression favors the transition from hyperplasia to neoplasia or the passage from a state of steady-state cellular division to a state of uncontrolled proliferation, characteristic of tumor cells. This state then influences the dissemination of cancer cells throughout the entire body (metastasis formation). On the other side, there is anti-angiogenesis mechanisms process interfere with blood vessel formation (Eichhorn, 2007).

Keywords: Cancer, Angiogenesis

Abbreviations: VEGF, vascular endothelial growth factor

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*Correspondence: EMAN Research and Testing Laboratory, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia.
E-mail: dhamora@yahoo.com

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Process of Angiogenesis

In normal physiological conditions, angiogenesis occurs primarily in the developing embryo, during wound healing and in response to ovulation. The abnormal rapid proliferation of blood vessels or pathological angiogenesis is implicated in over 20 diseases, including cancer, psoriasis and age-related macular degeneration (Schafer and Werner, 2008). The angiogenic process can be initiated by the release of angiogenic molecules, in response to a lack of oxygen, can influence inflammatory processes and can promote endothelial cells proliferation (Schugart et al., 2008). More than 20 endogenous positive regulators of angiogenesis have been described, including growth factors, matrix metalloproteinases, cytokines, and integrins. Growth factors, such as vascular endothelial growth factor (VEGF), transforming growth factors (TGF-beta), fibroblast growth factors (FGF), epidermal growth factor (EGF). Angiogenin can induce the division of cultured endothelial cells, thus indicating a direct action on these cells (Domenico et al., 2007). The endothelial cells that respond to these signals form the blood vessels by differentiating and by secreting matrix metalloproteases (MMP). Metalloproteases digest the blood-vessel walls enabling them to escape and migrate toward the site of the angiogenic stimuli. The protein fragments produced by the digestion of the blood-vessel walls intensify the proliferative and migratory activity of endothelial cells, which then form a capillary tube by altering the arrangement of their adherence-junction proteins through the cross-connection between adjacent channels. Regenerated capillaries from the arterioles and the venules will join, thus resulting in a continuous blood flow. A fine balance between factors that induce and inhibit the formation of blood vessels governs the normal regulation of

Author Affiliation:
EMAN Research and Testing Laboratory, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia

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ngiogenesis. When this balance is either destroyed or deregulated, it usually results in pathological angiogenesis, which causes increased blood-vessel formation in diseases that depend on angiogenesis (Vu et al., 2000).

Tumor Angiogenesis

Tumor angiogenesis is an uncontrolled and unlimited process essential for tumor growth, invasion, and metastasis. New vessels promote growth by bringing oxygen and nutrients and removing catabolites, whereas endothelial cell (EC) secrete growth factors for tumor cells and a variety of extracellular matrix (ECM)-degrading proteinases that facilitate invasion. An expanding endothelial surface also gives tumor cells more opportunities to enter the circulation and metastasize, whereas their ability to release antiangiogenic factors may explain the control exerted by primary tumors over metastasis (Ribatti et al., 2007)

Angiogenesis inhibitors and chemotherapy

Angioprevention was a term coined several years ago when it was proposed that angiogenesis inhibition was a common target of most cancer chemo preventive drugs. Angiogenesis inhibitors that inhibit blood vessels growth rather than tumor cells are unique cancer-fighting agents. In some cancers, angiogenesis inhibitors are most effective when combined with additional therapies (especially chemotherapy). Drug discovery has focused on the identification of the agents that can modulate individual targets. Some drugs with specific targets showed limited treatment efficacy, poor safety and the rapid development of resistance (Curèiæ et al., 2012; Critchfield et al., 2012). Due to these issues, clinical trials have confirmed success only with multicomponent therapies (Montero et al., 2012; Secord et al., 2012). Efforts have been made for the discovery of combinatorial therapies using new drugs and for the achievement of different synergistic effects (Wang et al., 2012; Urba et al., 2012). Many natural anti-angiogenesis compounds showed synergistic effects with cancer chemotherapies. Curcumin reveals synergistic inhibition on cell growth and an induction of apoptosis in human colon cancer cells when combined with chemotherapeutic drugs, such as bortezomib and 5-fluorouracil (Du et al., 2006). Grape seed extract (GSE) showed a synergistic effect with doxorubicin in the inhibition of the growth of estrogen-receptor–expressing MCF-7 cells as well as estrogen-receptor negative MDA-MB468 cells. The findings revealed that GSE could be used in combination with doxorubicin to enhance the efficacy of this drug (Sharma et al., 2007). Silibinin, a flavonolignan, is the major active component of the milk thistle plant (Silybummarianum). Oral administration of Silibinin, caused significant suppression of human non- small cell lung cancer (NSCLC) proliferation and A549 xenograft growth. It also enhanced the therapeutic response to doxorubicin, all while decreasing doxorubicin-induced adverse health effects (Singh et al., 2007). Several phytochemicals possess strong antiangiogenic activity, which plays an important role in their chemo-preventive properties (Tosetti et al., 2002; Béliveau et al., 2004). Tosetti showed that a series of substances proposed as possible cancer chemo-preventive agents showed antiangiogenic properties when tested in in vitro and in vivo angiogenesis models (Tosetti et al., 2002). Epigallocatechin gallate (EGCG), a flavonoid from green tea that possesses chemo-preventive activity in experimental and epidemiological studies, is a potent inhibitor of Matrix metalloproteinase MMP-2 and MMP-9. Angiogenesis has also been demonstrated to be a target for nonsteroidal anti-inflammatory drugs.

Chemoprevention and anti-angiogenesis

Chemoprevention, defined as the use of natural or synthetic chemical compounds to reverse, suppress or to prevent one or more of the biological events leading to the development of invasive cancer (Tsao et al., 2004). Chemopreventive compounds can be subdivided into antioxidant, antimutagenic, antiproliferative, anti-inflammatory and antiangiogenic. Antioxidant chemopreventive compounds prevent or delay oxidation at low concentrations, offering protection against oxidation mainly due to free radicals (Chipault et al., 1962). Antimutagenic chemopreventive compounds offer protection against DNA-damage induced mutations caused by mutagenic agents and slow cancer initiation (Shankel et al., 2000), while antiproliferative compounds interfere in the cell cycle, preventing and/or slowing down uncontrolled cancer cell division. Antiangiogenic compounds prevent proliferation of cancerous cells by reducing the amount of blood nutrients to the tumor environment. Sustained tumor growth is the result of loss balance between pro- and anti-angiogenic factors (Rose et al., 2000). Most chemo-preventive compounds currently in clinical use presumably act via multiple mechanisms, which are often unclear and sometimes controversial. The mechanisms of chemo-preventive agents can be grouped into two general classes: blocking agents and suppressing agents. Blocking agents prevent carcinogenic compounds from reaching or reacting with critical target sites by preventing the metabolic activation of carcinogens or tumor promoters via enhancing detoxification systems (free radical scavenging) and by trapping reactive carcinogens. Suppressing agents like vitamin D and related compounds, nonsteroidal anti-inflammatory drugs [NSAIDS] and vitamin A and retinoid prevent the evolution of the neoplastic processes in cells that could otherwise become malignant. Importantly, the mechanisms of action by which suppressing agents function are not well understood. (Wattenberg et al., 1996).

Cancer chemo-prevention is the use of pharmacological, natural, or dietary agents to inhibit the development of invasive cancer by blocking DNA damage caused by carcinogens or by arresting the progression of premalignant cells after damage has already occur-

red (Chemoprevention Working Group, 1999). A number of well-known chemo-preventative agents have antiangiogenic properties in vivo and in vitro. Classical angiogenesis assay systems, such as the chorioallantoic membrane assay (CAM), the corneal micropocket assay, and modified rat aortic ring assay, have been used to screen for biological activity of established chemo-preventive agents (Sharma et al., 2001; Kruger et al., 2001). The implementation of effective chemo-prevention strategies based on angiogenesis inhibition attained through dietary sources may decrease the numbers in a cost-effective and quality of life enhancing manner.

Conclusion

Years of research have shown that angiogenesis is a critical process for tumorigenesis. As the tumor necessitates an increased intake of nutrients and oxygen, novel chemicals and natural products that show antiangiogenic properties have stoked the fire in the field of anti-cancer drug design. Since natural and herbal molecules have shown biochemical efficacy in inhibiting several cancer-related processes including angiogenesis, it will be interesting to see how the these remedies will one day be used and perfected for cancer treatment.

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Author Contribution

Dhamraa W. A. made substantial contributions to the conception of the review.

Competing financial interests

The author(s) declare no competing financial interests.

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