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Original Articles

Antiangiogenic compounds: well-established drugs *versus* emerging natural molecules

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ABSTRACT

Angiogenesis is the natural and physiologic process of growing blood vessels from pre-existing ones. Pathological angiogenesis occurs when the precise balance of all the molecular pathways that regulate angiogenesis is disrupted, and this process is a critical step in many diseases, including cancer. A limited number of antiangiogenic synthetic drugs have been developed. However, due to toxicity and side effects issues, the search for alternative to existing drugs is ongoing. In this sense, natural molecules obtained from plants or macrofungi, have demonstrated extraordinary potential in the treatment of angiogenesis-related pathologies, specially taking into consideration its absence or very low toxicity, when compared to synthetic drugs. Using natural compounds as potential angiogenesis modulators is thus a promising field of research, supporting the creation of novel therapies able to reduce the use of drugs and associated side effects. In this review, the current status of antiangiogenic drugs and the wide variety of natural extracts and molecules with antiangiogenic capacities, as well as the angiogenesis molecular pathways and therapeutic targets, are presented. Finally, the challenges that need to be overcome in order to increase the use of natural compounds for clinical purposes are discussed.

1. An overview of angiogenesis

Angiogenesis is a biological process through which there is the formation of new blood vessels from pre-existing ones and occurs normally in the body under normal physiological conditions [1–3]. Angiogenesis naturally occurs during fetal development, tissue regeneration, wound healing and in the female reproductive cycle [1–4].

The trigger for normal angiogenesis is usually the detection of low levels of oxygen (hypoxia) by specific sensing mechanisms, in poorly perfused tissues, which stimulates the formation of new blood vessels to comply the cell metabolic requirements [5]. Alternatively, physiological angiogenesis is also triggered by mechanical tissue stretch [6].

Angiogenesis occurs in several steps, although some of these events may temporally overlap. The first step is the release of proteases that promote enzymatic degradation of the capillary basement membrane that triggers the migration of endothelial cells to the interstitial space and subsequent proliferation in cord-like form (sprout). The developing sprout elongates by proliferation of more endothelial cell and the two developing sprouts eventually fuse and form the lumen. Blood flow is then established and the newly formed blood capillary is stabilized through basement membrane deposition, pericyte recruitment and smooth muscle layer formation [7].

Although angiogenesis is a naturally occurring event, abnormal growth of new blood vessels is known to be involved in the development of various diseases including cancer, inflammation, eye illnesses, retinopathy, rheumatoid arthritis, among others [2,8]. Additionally, inadequate vessel preservation or growth may lead to ischemia causing myocardial infarction, stroke, and

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Abbreviations

AA-DLMs	Arachidonic Acid-derived Lipid
Ang-1	Angiopoietin
Akt	Protein Kinase B
ATP	Adenosine Triphosphate
BAEC	Bovine Aorta Endothelial Cells
CAM	Chick Chorioallantonic Membrane
Cdc37	Cell Division Cycle Protein 37
CDK4	Cyclin Dependent Kinase 4
CDK6	Cyclin Dependent Kinase 6
CDKs	Cyclin Dependent Kinases
CK2	Casein Kinase II
c-KIT	Tyrosine-Protein Kinase Kit
c-Met	Tyrosine-Protein Kinase Met
COX-2	Cyclooxygenase-2
CRC	Colorectal Cancer
DNA	Deoxyribonucleic Acid
EGCG	Epigallocatechin-3-gallate
EGFR	Epidermal growth factor receptor
eNOS	Endothelial Nitric Oxide Synthase
ERK	Extracellular Signal – Regulated kinase
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factors
GEJA	Gastro-Esophageal Junction Adenocarcinoma
GIST	Gastrointestinal Stromal Tumors
HCC	Hepatocellular Carcinoma
HIF-1	Hypoxia-inducible Factor
HMEC	Human Microvascular Endothelial Cells
Hsp90	Heat Shock Protein 90
HUVECs	Human Umbilical Vein Endothelial Cells
IFN	Interferon
IκB	Inhibitor of kappa B
IKK-β	Inhibitor of kappa B subunit β
IL-1	Interleukin - 1
IL-6	Interleukin - 6
iNOS	Inducible Nitric Oxide Synthase
LOX-5	5-Lipoxygenase
MAPK	Mitogen-Activated Protein Kinases
MMP	Matrix Metalloproteinases
MOLT-4	Human Leukemia Cells
MTC	Medullary Thyroid Cancer
NF-κB	Nuclear Factor kappa B
nNOS	Neuronal Nitric Oxide Synthase
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NSCL	Non-Small-Cell Lung Carcinoma
PDGF	Platelet Derived Growth Factor
PDGFR	Platelet Derived Growth Factor Receptor
PGA_2	Prostaglandin A2
PGD_2	Prostaglandin D2
PGE_2	Prostaglandin E2
PGF_2-α	Prostaglandin F2-α
PGI_2	Prostaglandin I2
PIK-3	Phosphoinositide 3-kinase
PKC	Protein Kinase C
PKC-α	Protein Kinase C α
RATEC	Rate Adipose Tissue Endothelial Cells
RCC	Renal Cell Carcinoma
RET|	Rearranged During Transfection
ROS	Reactive Oxygen Species
RTK	Receptor Tyrosine Kinase
STC	Soft Tissue Carcinoma
Tie	Angiopoietin receptor
TKI	Tyrosine Kinase Inhibitors
TNF-α	Tumor Necrosis Factor - α
TSP-1	Thrombospondin-1
VEGF	Vascular Endothelial Growth Factors
VEGFR-2	Vascular Endothelial Growth Factors Receptor - 2
YSM	Yolk Chic Sac Membrane

neurodegenerative diseases [1]. From a therapeutic point of view, in some diseases, including ischemic heart disease and peripheral arterial disease, the objective is to stimulate angiogenesis, while in other pathologies, including cancer, the goal is to inhibit abnormal angiogenesis.

The importance of angiogenesis in tumor development and metastases in cancer is well established. For tumor growth to occur, large amounts of nutrients and oxygen are necessary and, to overcome this situation, angiogenesis plays an important role in tumor development since it guarantees the survival of cells. Angiogenesis also facilitates the dissemination of tumor cells through the blood stream, achieving distant organs in the form of metastases [9,10]. Tumor angiogenesis occurs when tumor cells, as well as inflammatory cells aggregated to the tumor, produces angiogenesis factors that trigger the rapid development of angiogenesis [7,11]. Inhibition of tumor angiogenesis can thus decrease the blood flow, required for tumor development, and tumor cell growth would be ceased due to lack of nutrients and growth factors needed to support the formation of newly formed vessels [12].

Previous studies have identified and characterized numerous angiogenesis factors, both activators and inhibitors, which regulate angiogenesis. The most extensively studied angiogenesis regulators is vascular endothelial growth factor (VEGF) and the respective membrane receptors, mainly VEGFR-2, as they are recognized to play a major role in regulating physiological and pathological angiogenesis [13]. The first treatment that targeted tumor angiogenesis was monoclonal antibody bevacizumab, which acts by interacting and blocking VEGF interaction with its receptor. An alternative strategy to target VEGFR-2 is using small molecules like tyrosine kinase inhibitors (TKIs). This strategy resulted in the first clinically approved small molecule-like drugs that targeted tumoral angiogenesis: sunitinib and sorafenib [14,15]. VEGFR-2 inhibition is still being actively studied; it is considered an important strategy for angiogenesis inhibition [16] and towards the discovery of new anticancer drugs [17]. Many other angiogenesis therapeutic targets are currently being studied.

Natural compounds, present in medicinal and/or nutritional plants as well as in macrofungi sources, have stimulated a great interest from the pharmaceutical industry. Different natural compounds such as phenolic compounds, alkaloids, terpenoids among others, have shown strong antiangiogenic effects and can be considered as viable options to develop new strategies or drugs for targeting pathological angiogenesis. The low or even absent toxicity of these active compounds, make them an attractive alternative for human health maintenance. Chemoprevention is a promising anticancer approach with reduced secondary effects in comparison with synthetic drugs [18]. Chemoprevention consists in using other active molecules, such as naturally occurring anticancer agents, to inhibit or reverse some processes of carcinogenesis, including pathological angiogenesis [19]. The advent of diseases