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Review

Broad targeting of angiogenesis for cancer prevention and therapy

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ABSTRACT

Deregulation of angiogenesis – the growth of new blood vessels from an existing vasculature – is a main driving force in many severe human diseases including cancer. As such, tumor angiogenesis is important for delivering oxygen and nutrients to growing tumors, and therefore considered an essential pathologic feature of cancer, while also playing a key role in enabling other aspects of tumor pathology such as metabolic deregulation and tumor dissemination/metastasis. Recently, inhibition of tumor angiogenesis has become a clinical anti-cancer strategy in line with chemotherapy, radiotherapy and surgery, which underscore the critical importance of the angiogenic switch during early tumor development. Unfortunately the clinically approved anti-angiogenic drugs in use today are only effective in a subset of the

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patients, and many who initially respond develop resistance over time. Also, some of the anti-angiogenic drugs are toxic and it would be of great importance to identify alternative compounds, which could overcome these drawbacks and limitations of the currently available therapy. Finding "the most important target" may, however, prove a very challenging approach as the tumor environment is highly diverse, consisting of many different cell types, all of which may contribute to tumor angiogenesis. Furthermore, the tumor cells themselves are genetically unstable, leading to a progressive increase in the number of different angiogenic factors produced as the cancer progresses to advanced stages. As an alternative approach to targeted therapy, options to broadly interfere with angiogenic signals by a mixture of non-toxic natural compound with pleiotropic actions were viewed by this team as an opportunity to develop a complementary anti-angiogenesis treatment option. As a part of the "Halifax Project" within the "Getting to know cancer" framework, we have here, based on a thorough review of the literature, identified 10 important aspects of tumor angiogenesis and the pathological tumor vasculature which would be well suited as targets for anti-angiogenic therapy: (1) endothelial cell migration/tip cell formation, (2) structural abnormalities of tumor vessels, (3) hypoxia, (4) lymphangiogenesis, (5) elevated interstitial fluid pressure, (6) poor perfusion, (7) disrupted circadian rhythms, (8) tumor promoting inflammation, (9) tumor promoting fibroblasts and (10) tumor cell metabolism/acidosis. Following this analysis, we scrutinized the available literature on broadly acting anti-angiogenic natural products, with a focus on finding qualitative information on phytochemicals which could inhibit these targets and came up with 10 prototypical phytochemical compounds: (1) oleanolic acid, (2) tripterine, (3) silibinin, (4) curcumin, (5) epigallocatechin-gallate, (6) kaempferol, (7) melatonin, (8) enterolactone, (9) withaferin A and (10) resveratrol. We suggest that these plant-derived compounds could be combined to constitute a broader acting and more effective inhibitory cocktail at doses that would not be likely to cause excessive toxicity. All the targets and phytochemical approaches were further cross-validated against their effects on other essential tumorigenic pathways (based on the "hallmarks" of cancer) in order to discover possible synergies or potentially harmful interactions, and were found to generally also have positive involvement in/effects on these other aspects of tumor biology. The aim is that this discussion could lead to the selection of combinations of such anti-angiogenic compounds which could be used in potent anti-tumor cocktails, for enhanced therapeutic efficacy, reduced toxicity and circumvention of single-agent anti-angiogenic resistance, as well as for possible use in primary or secondary cancer prevention strategies.

1. Introduction to tumor angiogenesis

Vessel formation in both health and disease occur through either vasculogenesis – i.e. the recruitment of bone marrow-derived endothelial progenitor cells to form new vessels, angiogenesis – i.e. the sprouting and growth of new vessels from an existing vasculature or intussusception – i.e. the division or splitting of a blood vessel into two or more new vessels [1]. The most common pathway for neo-vessel growth in malignancy is angiogenesis (reviewed in [2]) and the process is therefore called tumor angiogenesis.

In 1971, Judah Folkman first advanced the hypothesis that tumor growth depends on angiogenesis [3]. According to this hypothesis, endothelial cells may be switched from a resting state to a rapid growth phase by a diffusible chemical signal emanating from the tumor cells. The switch depends on increased production of one or more positive regulators of angiogenesis, such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), interleukin-8 (IL-8), placental growth factor (PlGF), transforming growth factor-beta (TGFbeta), platelet derived growth factor (PDGF), angiopoietins (Angs) and others (reviewed in [4]). These can be exported from tumor cells, mobilized from the extracellular matrix, or released from host cells recruited to the tumor. The switch may also involve down-regulation of endogenous inhibitors of angiogenesis such as endostatin, angiostatin or thrombospondin (reviewed in [5]) and has thus been regarded as the result of tipping the net balance between positive and negative regulators. Mature microRNAs (miRNAs) can furthermore regulate the levels of pro- or anti-angiogenic gene expression at the post-transcriptional level (reviewed in [6]).

Angiogenic signals lead to the preferential differentiation of certain endothelial cells into so-called tip cells, which start to migrate and exist at the leading front of the growing vessels. A number of factors including VEGF receptor (VEGFR)-3 (for lymphatic endothelial cells), VEGFR-1 and–2 (for blood endothelial cells), PDGF-B, and the Notch ligand delta-like ligand (Dll)-4 have been shown to contribute to the endothelial tip cell phenotype [7,8]. In healthy angiogenesis during development for example, the number of tip-cells are limited leading to an orderly and organized expansion of the vasculature. Endothelial cells located behind the tip cell, so-called stalk cells, express other factors such as VEGFR-1 and Notch-1 and -4 which are important for inducing a quiescent state of these cells [9,10], maturation of the vascular wall, lumen formation and to support perfusion. However, in pathological angiogenesis including tumor angiogenesis this process is usually disrupted by either excess production of pro-angiogenic signals, lack of angiogenesis inhibitors, path-finding signals or maturation factors, thus leading to excessive tip-cell formation and migration of endothelial cells [11,12], which do not assume a quiescent phenotype associated with a healthy vasculature.

1.1. Structural and dysfunctional features of tumor blood vessels

As a result of the imbalance of angiogenic activators and inhibitors, tumor blood vessels display many structural and functional abnormalities including unusual leakiness (reviewed in [13]), potential for rapid growth and remodeling [14], high tortuosity and sinusoidal appearance (reviewed in [13]), poor coverage by vascular supportive cells including pericytes and smooth muscle cells [15], lack of arterial or venous identity leading to chaotic blood flow, poor functionality and perfusion [16], incorporation of tumor cells into the endothelial wall, alternatively differentiation of tumor stem-like cells to endothelial cells which contribute to the tumor vasculature – a process known as vascular mimicry [17]. These phenotypes, which can be considered "hallmarks of the tumor vasculature", mediate the dissemination of tumor cells in the bloodstream and maintain the pathological characteristics of the tumor microenvironment.

Tumor vessel density is furthermore very heterogeneous: the highest values are found in the invading tumor edge, where the density is 4–10 times greater than inside the tumor and