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Hot Topic

Role of angiogenesis in the pathogenesis of cancer

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ABSTRACT

It has been recognized for decades that angiogenesis is an important event in tumor growth and metastasis; the concept of the "angiogenic switch," whereby tumors acquire the ability to grow exponentially and disseminate beyond their primary site, is one of the central components in our understanding of cancer. A vast network of signaling molecules and receptors that are involved in the regulation of angiogenesis have been identified and characterized; most notably, the vascular endothelial growth factor (VEGF) family. Indeed, the VEGF family of growth factors and receptors has become a prototype for our understanding of angiogenesis during early development and in pathological conditions such as cancer. The specific inhibition of key regulatory molecules including VEGF-A (such as with bevacizumab treatment) has been recognized as a useful strategy to reduce tumor growth and progression in several tumor types. Nevertheless, the contribution of other members of the VEGF family, other signaling pathways, and also endogenous angiogenic inhibitors to tumor angiogenesis, is beginning to emerge. The diversity of pathways and molecules involved in the regulation of angiogenesis in both normal development and cancer will likely offer many more prospects for successful therapeutic intervention.

Historical perspective on angiogenesis

Angiogenesis, the process in which new capillaries grow from existing blood vessels, has long attracted interest due to its role in health and disease. The first recorded observations of angiogenesis are thought to be those of the 18th-century Scottish surgeon and anatomist, John Hunter, who made detailed observations on new blood vessels forming at sites of injury or inflammation.[1] In 1907, Emil Goldmann described the abnormal characteristics of blood vessels in the vicinity of the tumor.[2] In the following decades, the study of tumor angiogenesis advanced further — specifically, with the use of implanted transparent chambers in a rabbit's ear and contrast media, which made it possible to study the morphologic characteristics of developing vessels in living animals.[3,4]

In 1971, Judah Folkman and colleagues proposed that tumor growth and metastasis were angiogenesis dependent, and suggested that blocking angiogenesis could be a viable strategy to arrest tumor growth.[5] In Folkman et al.'s landmark article, the isolation of a diffusible tumor angiogenesis factor was described.[5] It was proposed on the basis of these findings that in the absence of angiogenic factors, tumors remained dependent on diffusion of nutrients from the extravascular space and were unable to grow beyond 3–4 mm in diameter. Therefore, the onset of angiogenesis could be identified as an essential step in cancer progression. The authors suggested that any means of blocking this angiogenesis factor might be of therapeutic potential for halting tumor growth.[5]

Subsequent observations in both experimental and human tumor models led to the concept of the "angiogenic switch," whereby tumors acquire the ability to grow exponentially and disseminate beyond their primary site, as a discrete, rate-limiting step in the development of many tumors, and efforts to characterize these putative tumor angiogenic factors became an expanding research area.[6] Improved isolation techniques, such as heparin affinity chromatography, made possible the isolation of the vascular endothelial growth factor (VEGF), which had potent mitogenic activity specific to vascular endothelial cells.[7,8] Later, molecular cloning and sequencing led to the unexpected finding that VEGF and vascular permeability factor (VPF) were one and the same.[9–11]

Importance of angiogenesis in physiologic processes

Angiogenesis is a complex process that requires coordinated activity of a variety of vascular components: the division of endothelial cells, degradation of vascular basement membranes and the surrounding extracellular matrix, and endothelial cell migration.[12] Pro-angiogenic molecules are maintained in a dormant state and upregulated when angiogenesis is required for physiologic processes, such as reproduction, embryogenesis, organ differentiation,

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and tissue repair.[13,14] Under physiological conditions, external stimuli, including hypoxia, hypoglycemia, and mechanical stress, activate the highly ordered angiogenesis network.[15] Hypoxia, the most-studied activating agent, upregulates hypoxia-inducible factor (HIF-1),[14–16] mammalian target of rapamycin (mTOR), endoplasmic reticulum kinases, and soluble guanylate cyclases, which leads to the development of vasculature and additional organs during embryogenesis.[14] In adults, angiogenesis is involved in the maintenance of the vasculature in wound healing, ischemia, ovarian function, as well as endometrium proliferation during the reproductive cycle and in placenta formation.[14]

Angiogenesis in the pathogenesis of cancer

Ischemic and hypoxic signals initiate many of the processes that are associated with physiological angiogenesis.[14] During tumor angiogenesis, however, the angiogenic network is uncontrolled and remains upregulated due to a shift between pro-angiogenic and antiangiogenic factors, and between angiogenic proteins of the tumor and those of the host.[13] Tumor growth beyond 1–2 mm diameter becomes possible due to the hypoxic microenvironment, which activates the angiogenic network and results in the sprouting of blood vessels from the surrounding tissues into the tumor.[6] Angiogenic signaling within the tumor stroma is associated with tumor-associated fibroblasts, macrophages, mast cells, and myeloid cells expressing cell surface markers CD11b and Gr1.[14]

Pathological angiogenesis is characterized by an increase in proliferating endothelial cells and by atypical morphology of the tumor vasculature.[12,17] The hierarchy of arterioles, capillaries, and venules that is associated with normal vasculature is absent in that of tumors.[17] Endothelial cells, pericytes, smooth muscle cells, and basement membrane that comprise tumor blood vessels are also abnormal.[17] Endothelial cells do not form the tight monolayers associated with normal blood vessels, and the tumor vasculature remains leaky, which contributes to the high interstitial pressure in most tumors.[17] Furthermore, pericytes are only loosely attached to endothelial cells in the tumor vasculature and may weaken the vessel wall, increasing the risk of hemorrhage.[17] In addition, the vascular basement membrane has irregular thickness and several surplus layers, and is also only loosely associated with endothelial cells.[17]

Angiogenesis: a network of signaling pathways

The control of the complex and dynamic process of angiogenesis involves multiple interacting antiangiogenic and proangiogenic signals, including growth factors, angiopoietins, junctional molecules, oxygen sensors, endothelial sensors, and others.[15,18] The role of the VEGF family is widely recognized as key in tumor angiogenesis.

The VEGF family

The growth factors VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) comprise the VEGF family (Table 1).[19–21] The different members of the VEGF family differ in binding specificities to different receptors (Fig. 1), and these differences may account for their widely differing physiological functions.[22]

Expression of VEGF is highly regulated by hypoxia, providing a feedback mechanism to compensate reduced tissue oxygenation via the formation of new blood vessels. The regulation of VEGF expression by hypoxia is mediated by the family of HIF, which increases transcription of the VEGF gene.[16] Hypoxia also upregulates VEGF levels by stabilizing messenger RNA[23] and also via multiple mechanisms not involving HIF.[24] Cytokines such as epidermal growth factor (EGF), transforming growth factor-beta (TGF-beta), and other influences (e.g., p53 expression) may also increase VEGF expression by a number of different mechanisms.[25] Conversely, the antiangiogenic and antitumor properties of interferon alfa may be mediated, at least in part, by inhibition of VEGF gene transcription.[26]

VEGF-A

VEGF-A, previously known as VEGF, was the first VEGF family member to be isolated, and is the best studied of them.[15,27] Increased intratumoral VEGF-A expression is observed in many different tumor types, including those of the lung, breast, gastrointestinal tract, kidney, bladder, and ovary. These increased levels have been correlated with poor prognosis and enhanced recurrence risk.[15,27] The principal actions of VEGF-A include potent mitogenic actions on vascular endothelial cells, activation of enzymes involved in extracellular matrix degradation, pro-survival effects on endothelial cells via the inhibition of apoptosis, mobilization of bone marrow endothelial precursors, modulation of endothelial migration, and increase in vascular permeability.[15]

VEGF-A mediates these biologic effects via its interaction with tyrosine kinase (TK) receptors VEGFR-1 and VEGFR-2 (Fig. 1). Although VEGFR-1 binds VEGF-A with approximately 10 times the affinity of VEGFR-2, its kinase activity is less than that of VEGFR-2. The interaction of VEGF-A with VEGFR-2 seems to be required for most of the biologic effects of VEGF (Fig. 2).[15,27–32] There is evidence that VEGFR-1 is indeed upregulated in some tumor types, suggesting a role in tumorigenesis. Colon cancer cell lines expressing VEGFR-1 showed increased migration, invasiveness, and colony formation, but not increased proliferation when stimulated by either VEGF-A or VEGF-B. These effects were specifically inhibited by anti-VEGFR-1 antibodies.[33] Expression of VEGFR-1 has also been detected in Wilms's tumor, where it has been correlated with microvessel density as well as clinical progression and survival.[34] VEGF-A also interacts with the neuropilin (NRP) receptors on some cell types. NRP1 can enhance the interaction of VEGF-A with VEGFR-2, leading to increased signaling.[27,35] Studies have also suggested that endogenous VEGF-A is a physiologic negative regulator of adult erythropoeisis, and that systemic inhibition of VEGF-A leads to increased hepatic production of erythropoietin (Epo) through a mechanism involving VEGF-A/VEGFR-2 – dependent endothelial cell – hepatocyte cross-talk.[36] Nonetheless, erythrocytosis and increased hepatic Epo production have been identified as potential markers of potent VEGF inhibition.[36] Besides tumor hypoxia, inflammatory cells in the tumor microenvironment can also serve as sources of VEGF-A.[16] Increased expression of VEGFRs in tumor cells also supports a role for VEGF-A as a paracrine factor to stimulate angiogenesis in cancer.[15,27]

VEGF-B and PlGF

VEGF-B and PlGF also interact with VEGFR-1, but neither interacts with VEGFR-2 (Fig. 1).[37–39] As the interaction of VEGF-A with VEGFR-2 is believed to be of utmost importance in the pro-angiogenic effects of VEGF, the potential roles of VEGF-B and PlGF in tumor angiogenesis have received less attention and remain somewhat controversial.[22]

VEGF-B has been shown to act as a survival rather than pro-angiogenic factor.[40] Genome-wide profiling showed that VEGF-B upregulated the expression of a number of pro-survival genes, and that these pro-survival effects were mediated by both VEGFR-1 as well as NRP-1, which has also been shown to bind VEGF-B (Fig. 1).[40,41] These findings support the hypothesis that NRP1 may serve to modulate and/or potentiate the effects of VEGF-B and its receptor VEGFR-1 when both are expressed.[41] In animal