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VIEWPOINT

Regulators of Angiogenesis: Stimulators, Inhibitors, and Extracellular Matrix

With very few exceptions, tissues need blood vessels in order to develop and survive. The aberrant growth of blood vessels, as occurs in cancer, can lead to undesired cell growth. Given the physiological and pathological consequences of blood vessel development, it is no wonder that in the last 20 years, there has been an intense interest in elucidating the mechanisms that regulate angiogenesis. Much of the focus has been on the identification of factors that can either stimulate or inhibit angiogenesis. The underlying rationale in identifying angiogenic factors has been the goal of being able eventually to modulate angiogenesis in vivo. The ability to enhance vascularization of tissue would be of major benefit in the healing of damaged tissue such as skin wounds or infarcted hearts. On the other hand, the ability to inhibit angiogenesis would be of therapeutic use in controlling the growth of vascular tumors. What has been surprising is the complexity of angiogenesis and the myriad of factors that control it. Quite a few stimulators and inhibitors of angiogenesis have been identified that modulate the ability of endothelial cells in vitro or capillaries in vivo to either proliferate or to migrate or to do both. Following is a brief overview of the role of stimulators, inhibitors and extracellular matrix in the angiogenic process.

Angiogenic stimulators include basic fibroblast growth factor (bFGF), platelet-derived endothelial cell factor (PD-ECGF), and vascular endothelial growth factor (VEGF), which is also known as vascular permeability factor (VPF). These growth factors are endothelial cell mitogens in vitro and are thought to act directly by stimulating the endothelial cell in a capillary to migrate and proliferate. Other angiogenic stimulators that are not mitogenic for endothelial cells in vitro are thought to act indirectly by stimulating secondary cells such as monocytes/macrophages to release the direct-acting endothelial cell growth factors. These include transforming growth factor beta (TGF-beta) and tumor necrosis factor alpha (TNF-alpha). Angiogenin is also an angiogenesis factor that is not mitogenic for endothelial cells in vitro and therefore is thought to act indirectly but how this occurs is not known. A third class of angiogenic factors includes growth factors that stimulate endothelial cell migration in vitro and capillary migration in vivo but not proliferation. Examples are platelet-derived growth factor (PDGF-BB) and angiotropin. The redundancy in angiogenic stimulators is apparent and suggests complex mechanisms of angiogenesis regulation. One might speculate that the various stimulators might be expressed differentially, and temporally in specific cells and tissues. For example, PD-ECGF, PDGF, and TGF-beta which are found in platelets might be released at the site of injury with the role of enhancing tissue healing. On the other hand, FGF which is cell and matrix-associated might be released by the damaged tissue itself in an attempt at self healing.

Progress has also been made in identifying angiogenic inhibitors, although not to the same extent as the stimulators. One such inhibitor has been isolated from cartilage, an avascular tissue long suspected of not being able to produce blood vessels due to the presence of inhibitory factors. The cartilage-derived inhibitor of angiogenesis has been identified as a member of the tissue inhibitor of metalloproteinases (TIMP) family. It is an inhibitor of collagenase and the speculation is that inhibition of endothelial cell collagenase might prevent capillaries from invading the surrounding stroma, thereby blocking capillary migration. Another angiogenesis inhibitor is thrombospondin. Interestingly, it has been shown that the production of thrombospondin is dependent on the expression of an active tumor suppressor gene. Thus it appears that tumor-mediated angiogenesis and the consequent vascularization of tumors might be linked to the inability of tumor cells to produce thrombospondin, an angiogenesis inhibitor. TGF-beta presents somewhat of a paradox. Although a potent angiogenesis factor in vivo, it is an inhibitor of endothelial cell proliferation and migration in vitro. The speculation is that TGF-beta stimulates inflammatory angiogenesis by recruiting

monocytes/macrophages that express angiogenic stimulators. However, its direct effect is to prevent endothelial cell growth consistent with the inhibitory effects of TGF-beta on the growth of many cell types. An interesting observation is that TGF-beta induces production of thrombospondin, an endothelial cell inhibitor, thereby suggesting a possible mode of TGF-beta action. Platelet-factor 4 (PF4) is an angiogenesis inhibitor. Its presence in platelets which also contain the angiogenic stimulators PD-ECGF and PDGF suggests that these cells, and probably other cells as well (for example, macrophages), carry both angiogenic stimulators and inhibitors and that a balance of factors is a control element in blood vessel growth. There is also an angiogenesis inhibitor not found in the body but which is produced by fungi. Unlike most other angiogenic factors which are polypeptides, the fungal inhibitor, known as fumagillin, is a complex lipid. Synthetic analogues of fumagillin have been shown to inhibit tumor angiogenesis and are therefore promising anti-cancer agents. Many questions surround the inhibitors. For example, do they directly counteract angiogenic stimulators? Do they work directly at the level of the endothelial cells and if so how and if not where?

A very important component in regulating angiogenesis is the extracellular matrix (ECM) of endothelial cells. While soluble stimulators and inhibitors work at relatively long range, ECM, through its binding of cells, acts locally to modulate the response of endothelial cells to the external factors. Besides matrix proteins such as laminin, collagen, and fibronectin, bFGF itself is a component of sub-endothelial cell ECM. It is thought to be sequestered in ECM as a stable complex with heparan sulfate proteoglycan. One thought is that during injury to blood vessels, release of bFGF leads to a self-repair process; bFGF released during injury from ECM produced by cells may mediate repair by inducing angiogenesis. At another level, ECM might provide a barrier to angiogenesis. Degradation of matrix by endothelial cell proteinases is thought to facilitate capillary migration, hence the interest in collagenase and proteinase inhibitors as anti-angiogenesis factors. The angiogenic stimulator, bFGF, induces plasminogen activator (PA) and collagenase production by endothelial cells suggesting that in part it is angiogenic by stimulating ECM degradation. On the other hand, the inhibitory effects of TGF-beta on endothelial cell growth have been attributed to enhanced ECM production and to quantitative and qualitative changes within the ECM. Net increase in ECM production is the result of TGF-beta induction of plasminogen activator inhibitor (PAI) and down-regulation of PA. It is speculated that enhanced ECM production is a barrier to blood vessel migration and development. All in all, it is clear that, whether it is a repository of angiogenic factors or whether it is produced or degraded in response to these factors, ECM is a critical control point in angiogenesis.

A more detailed analysis of blood vessel regulation can be found in the seven Prospects on angiogenesis as presented in this issue. These include articles describing the angiogenic properties of PD-ECGF (Heldin, Usuki, and Miyazono), basic FGF (Mignatti and Rifkin), VEGF (Ferrara, Houck, Jakeman, Winer, and Leung), VPF (Connolly), TGF-beta (RayChaudhury and D'Amore), the TIMP-like cartilage-derived angiogenesis inhibitor (Moses and Langer), and ECM (Ingber). Together, these articles should provide an in-depth analysis of how angiogenesis is regulated by various angiogenic factors.

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