Angiostatic and Angiogenic Factors

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Abstract
Both diminution of angiostatic and increment of angiogenic factors seem to contribute to neovascularization in the eye under pathologic conditions. They are presented here separately. The involved proteins can change their role during the process of neovascularization from promoters to inhibitors and vice versa. Angiostatic factors can be divided into passive, active, unspecific and specific ones. Some of them act during neovascularization as members of feedback loops by modifying the effects of their angiogenic counterparts. Among the angiogenic factors VEGF is the most important. Nevertheless other stimulating proteins exist in large numbers. Together with their static counterparts they form a complex network which controls neovascularization under physiologic as well as pathologic conditions.

A short introduction into the topics of angiostatic and angiogenic factors is given. All molecules mentioned and their interactions within the organism will be discussed in the following article.

Angiostatic Factors in the Eye

Under healthy conditions the vascular system of the eye is thought to be stable. Normal angiogenesis is concluded during early childhood and only reappears under certain pathologic conditions. While one common trigger of neovascularization in many eye diseases is ischemia, neovascularization can also occur without significant ischemia. This is the case in wet age-related macular degeneration (AMD). However, hypoxia and/or alterations of the perfusion are still under discussion to be an important cofactor in the pathogenesis of this disease entity.

In ischemic neovascularization, new capillaries typically sprout from branches of the retinal arteries. In contrast, the neovascularization in AMD originates from the
choriocapillary layer. The physiological stability of the ocular vascular system is an equilibrium between angiostatic and angiogenic factors. The vasculature is stable as long as the angiostatic factors are ahead. Pathologic conditions such as ischemia or inflammation shift the balance towards angiogenic factors which are released by the damaged cells. On the other hand the unpredictable appearance of neovascularization during dry AMD which cannot be prevented by anti-inflammatory treatment strongly points out that also a loss of angiostatic factors alone can lead to instability of the constructive vascular boundaries of the eye.

The strong angiostasis that is crucial for the function of the eye is maintained by angiostatic factors in every involved tissue starting from the specialized guards of the blood-retinal barrier down to unspecific ingredients of the blood fluid. The angiostatic effect is not only locally distributed but also stepwise during stages of angiogenesis. Due to the defensive nature of static concepts, not only active components such as inhibitor proteins but also passive stabilizing members of the extracellular matrix can be accounted to the angiostatic system.

Thus, collagens, elastins and fibrin constitute a first barrier for angiogenesis. These molecules have to be actively degraded and the respective proteases are controlled by protease inhibitors. Tissue inhibitors of metalloproteinases are specific metalloproteinase inhibitors while the serum component α₂-macroglobulin unspecifically inhibits metalloproteinases. Another protein that interferes with pericellular proteolysis required for migration and proliferation of endothelial cells is thrombospondin which is present in platelet granules and is released following platelet activation. If proteolytic degradation of capillary basement membranes occurs, a fragment of the collagen type 18 called endostatin is released. It specifically inhibits proliferation of endothelial cells and angiogenesis.

Other passive components of vascular stability are the VE cadherins that are involved in intercellular tight junctions – the constituting basis of the blood-retinal barrier. VE cadherins are members of a large family of adhesion proteins called cadherins that build intercellular contacts like desmosomes throughout the body. VE cadherins have to be degraded before angiogenesis can occur. Their degradation is triggered by vascular endothelial growth factors (VEGF) via the VEGFR-2 receptor.

More active components of vascular structural stability of the eye are proteins that are secreted by the cells of the blood-retinal barrier. A protein that maintains stability after maturation of newly grown capillaries is angiopoietin-1. It is produced by pericytes. Its presence in mature capillaries improves continuity of the basal membranes and the adherence of pericytes to endothelial cells. During angiogenesis it promotes capillary growth. It is antagonized by angiopoietin-2 which binds to the same endothelial cell-specific receptor Tie-2. TGF-β has among its many other effects a similar role as it is secreted by pericytes and stabilizes the basal membrane of newly built capillaries.

Pigment epithelium-derived factor is a cytokine that despite its name is produced in many human cells including endothelial cells and retinal pigment epithelial cells
where it was originally detected. Among other effects it is a potent inhibitor of angiogenesis. It also has immunomodulatory features and contributes by this indirectly to prevention of neovascularization.

The vasoinhibins act as negative feedback regulators upon the effect of VEGF. They are upregulated in endothelial cells by VEGF and specifically inhibit migration and proliferation of these. Angiostatin also specifically inhibits proliferation of endothelial cells. It is a fragment of plasminogen and therefore exists as a plasma factor throughout the body.

**Angiogenic Factors**

The growth of new blood vessels is an important natural process occurring in the body, both in health and disease. Angiogenesis is a physiological process involving the growth of new blood vessels from preexisting vessels whereas vasculogenesis describes the formation of vascular structures from circulating or tissue-resident endothelial stem cells (angioblasts) which proliferate into de novo endothelial cells.

The healthy body controls angiogenesis through a series of ‘on’ and ‘off’ switches. The main ‘on’ switches are known as angiogenesis-stimulation growth factors, or simply angiogenic factors. Stimulation of angiogenesis is performed by various angiogenic proteins, including several growth factors, whereas the VEGF family has been demonstrated to be a major contributor to angiogenesis. Additionally, a large number of mediators exist which are involved in angiogenesis like insulin-like growth factor, the family of fibroblast growth factor, interleukins, angiopoietins, epidermal growth factor, transforming growth factors, platelet-derived growth factor, tumor necrosis factor-α and vascular endothelial cadherin.

The balance between angiogenesis and inhibitors of new vessel growth is controlled by a sophisticated interaction between different factors and mediators which will be described explicitly in the following chapter.

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