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Review

Glycation: The angiogenic paradox in aging and age-related disorders and diseases

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ABSTRACT

Angiogenesis is generally a quiescent process which, however, may be modified by different physiological and pathological conditions. The "angiogenic paradox" has been described in diabetes because this disease impairs the angiogenic response in a manner that differs depending on the organs involved and disease evolution. Aging is also associated with pro- and antiangiogenic processes. Glycation, the post-translational modification of proteins, increases with aging and the progression of diabetes. The effect of glycation on angiogenesis depends on the type of glycated proteins and cells involved. This complex link could be responsible for the "angiogenic paradox" in aging and age-related disorders and diseases. Using diabetes as a model, the present work has attempted to review the age-related angiogenic paradox, in particular the effects of glycation on angiogenesis during aging.

Contents

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1. Introduction

Glycation, the post-translational modification of proteins, results on a progressive accumulation of protein damage during aging with multiples effects including modifications on angiogenesis. Angiogenesis, which can be defined as the formation of new capillaries via endothelial cell (EC) proliferation, migration and sprouting, generally remains quiescent after the developmental phase. However, it may become activated in response to exercise or during wound healing. Several pathological states are associated with modifications in the angiogenic process. Cancer has been the focus of much study in this regard, as tumor survival and growth need an important blood supply (Carmeliet and Jain, 2011). Diabetes also modifies angiogenesis, depending on the organs involved and disease progression. Angiogenesis is also affected by aging. Aging is associated with both pro- and anti-angiogenic processes (Edelberg and Reed, 2003; Lim et al., 2012). Glycation, increases in the course of aging and diabetes and could be partly responsible for the paradoxical angiogenic effects observed. However, it should be noted that differences have been found between angiogenesis in age-related and diabetes-associated disease. Taking diabetes as a model, the present authors have therefore proposed to review the age-related angiogenic paradox and in particular the effects of glycation on angiogenesis during aging.

2. Angiogenesis

As mentioned above, angiogenesis can be defined as the formation of new capillaries through endothelial cell (EC) proliferation, migration and sprouting. It involves extracellular matrix (ECM) remodeling, EC proliferation, migration and tube-like structure formation. Angiogenesis is therefore a complex process which is regulated by pro- or antiangiogenic growth factors (principally vascular endothelial growth factor [VEGF]), cytokines, cells and the ECM (Carmeliet and Jain, 2011). Even though ECs are the main cells implicated in angiogenesis, many other "environmental" cells also play a key role in the angiogenic process, essentially through VEGF, resulting in an "angiogenic cross-talk" between the ECs and the environmental cells (Fig. 1).

After the developmental phase, the angiogenic process becomes quiescent due to the action of antiangiogenic molecules that counterbalance proangiogenic factors. During adulthood, the triggering factors for angiogenesis are chronic ischemia or hypoxia. These conditions modify the balance between pro- and antiangiogenic factors and result in neoangiogenesis. The molecular mechanisms underlying neoangiogenesis include several steps (Fig. 2): first of all, angiogenic factors stimulate the quiescent vessels. Matrix remodeling, increased vessel permeability, pericyte detachment and the loss of tight junctions lead to vessel dilation and allow "tip" EC selection by angiogenic factors. Then the "tip" cells ensure branch formation, driven by signals and adherence to the ECM (semaphorins, ephrins, integrins). Behind the tip cells, the proliferation, elongation and sprouting of "stalk" cells lead to the formation of perfused neovessels. Stabilization of the neovessels is ensured by pericyte recruitment and maturation and basement membrane deposition. After fusion of the neighboring branches, stabilizing factors brought by the blood flow into the neolumen lead to a quiescent EC phenotype with new EC–EC junctions, pericyte maturation and vascular maintenance signaling (Carmeliet and Jain, 2011).

In contrast to angiogenesis, arteriogenesis involves the remodeling of pre-existing arterio-arteriolar anastomoses into fully developed and functional arteries. While angiogenesis is induced by hypoxia, arteriogenesis is triggered by physical factors, most importantly fluid shear stress which is frequently linked to vessel stenosis and occlusion (Heil et al., 2006). The re-routing of blood flow into small arterio-arteriolar anastomoses leads to an increase in arterial wall thickness and to the enlargement of artery size through the active proliferation of vessel wall components (ECs, smooth muscle cells, fibroblasts). Monocyte activation and recruitment also play a critical part in arteriogenesis via the secretion of proangiogenic cytokines. The time course relating to these two processes is different: arteriogenesis is estimated to last for a maximum of a few weeks, whereas angiogenesis takes place over a period ranging from several months to years (Waltenberger, 2007).

The main proangiogenic factors involved belong to the VEGF family (Ferrara et al., 2003). Alternative exon splicing of VEGF-A (usually called VEGF) leads to the formation of four isoforms: $VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$ and $VEGF_{206}$, all of which have different origins, diffusion and receptor-binding properties. $VEGF_{165}$ seems to constitute the most efficient compromise between these four forms. Other genes (VEGF-B, -C or -D) play a less important part in

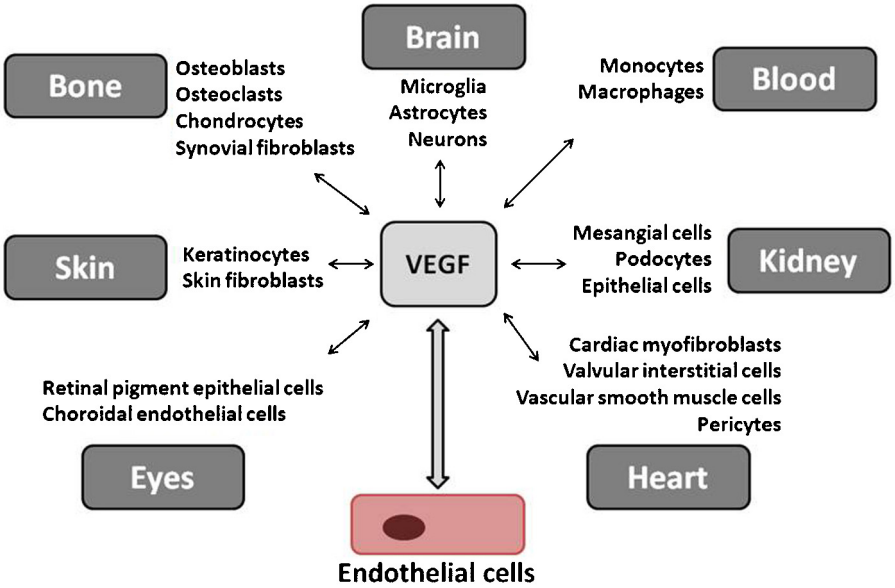

Fig. 1. The "angiogenic cross-talk". VEGF plays a central role in communication between the "environmental cells" and the ECs during angiogenesis. VEGF: vascular endothelial growth factor.