Angiogenesis in Diabetic Nephropathy

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Summary: Angiogenesis, the formation of new blood vessels from pre-existing vasculature, plays a key role in both physiologic and pathologic events, including wound healing, cancer, and diabetes. Neovascularization has been implicated in the genesis of diverse diabetic complications such as retinopathy, impaired wound healing, neuropathy, and, most recently, diabetic nephropathy. Diabetic nephropathy is one of the major microvascular-associated complications in diabetes and is the leading cause of end-stage renal disease worldwide. In this review we describe the major factors involved in the pathologic glomerular microvascular alterations in response to hyperglycemia and the possible use of anti-angiogenic therapies for the treatment of diabetic nephropathy.
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Diabetic nephropathy represents a major cause of morbidity and mortality in type 1 and type 2 diabetic subjects and has become the leading cause of end-stage renal disease worldwide. Currently there is no specific therapy for this condition, which almost invariably progresses to end-stage renal failure. One of the hallmarks of diabetic nephropathy is glomerular microvascular injury, which potentially may be a therapeutic target for this devastating medical condition. In this review we describe (1) the major steps involved in angiogenesis, (2) the pathologic glomerular vascular changes observed in diabetic nephropathy, and (3) the possible use of anti-angiogenic therapy for the treatment of diabetic-induced renal vascular damage.

ANGIOGENESIS

Angiogenesis is the formation of new blood vessels from pre-existing vasculature. This process plays a key role in both physiologic and pathologic events, including embryonic development, menstruation, wound healing, tumor growth, and diabetes. Angiogenesis is a multistep process that requires at least 4 independent events by endothelial cells, including detachment from basement membranes, proliferation, migration, and maturation.[1] Normally these events are regulated tightly by both pro-angiogenic and anti-angiogenic factors, however, in pathologic events such as diabetes there is increased synthesis of pro-angiogenic factors with concomitant down-regulation of anti-angiogenic molecules. This leads to increased proliferation and migration of endothelial cells, resulting in the formation of immature and leaky vessels.

Proangiogenic Factors

The soluble molecules vascular endothelial growth factor (VEGF) and angiopoietins (Ang 1 and Ang 2), are the best-characterized growth factors that play a role in angiogenesis. The VEGF family consists of at least 4 members, VEGF-A, -B, -C, and -D.[2] VEGF-A, the most predominant, consists of at least 8 isoforms, with VEGF165 the major form expressed in humans (VEGF 164 in mouse). VEGF was first described as a vascular permeability factor because of its ability to induce leaky vessels. It exerts its actions by binding 3 different receptors selec-

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tively expressed on endothelial cells, VEGF receptor I (ie, VEGFR1, Flt-1), VEGF receptor 2 (ie, VEGFR2, Flk-1), and VEGF receptor 3 (VEGFR3).[3] Flt-1 is required for the recruitment of hematopoietic precursors and the migration of monocytes and macrophages, whereas Flk-1 and VEGFR3 are essential for the functions of vascular endothelial and lymphendothelial cells, respectively.[3] VEGF is probably the most potent angiogenic factors and its up-regulation often is observed in pathologic conditions, including cancer, rheumatoid arthritis, and diabetes. Up-regulated VEGF synthesis is accompanied by increased endothelial cell migration, proliferation, and formation of immature vessels characterized by leakiness and decreased vascular resistance.

The angiopoietins belong to a family of at least 4 members, with Ang 1 and Ang 2 being the most predominant.[4] Both Ang 1 and Ang 2 exert their action by binding the same receptor Tie-2, selectively expressed on endothelial cells. Interestingly, Ang 1 and Ang 2 exert opposite effects on endothelial cell function. Although Ang 1–mediated signaling via Tie-2 leads to vessel maturation, quiescence, and reduced leakage,[5,6] Ang 2 blocks the Ang 1/Tie-2 signal resulting in increased angiogenesis, vessel instability, and consequent leakage.[7,8] Moreover, although Ang 1 promotes endothelial cell adhesion, spreading, and formation of focal contacts, Ang 2 enhances endothelial cell migration and tubulogenesis. Ang 1 and Ang 2, unlike VEGF, are not considered complete angiogenic factors because they cannot trigger angiogenic responses by themselves, but rather they positively or negatively modulate VEGF-induced endothelial cell function.[9] Interestingly, Ang 2 expression can be up-regulated by VEGF[10] and it enhances VEGF-mediated angiogenesis.[4] In pathologic events, such as cancer or diabetes, increased VEGF synthesis often is accompanied by increased Ang 2 levels with decreased and/or unchanged levels of Ang 1.

Anti-angiogenic Factors

To ensure that there is not an overproduction of blood vessels there are endogenous inhibitors of angiogenesis that can be classified into 2 major categories: proteolytic fragments and gene products.[11] Among the proteolytic fragments, extracellular matrix–derived and plasminogen-derived fragments have been shown to inhibit angiogenesis by inhibiting endothelial cell migration, proliferation, and tubulogenesis. Some of these fragments include angiostatin (a cleavage product of circulating plasminogen), endostatin (a cleavage product of collagen XVIII), the α1NC1 domain of collagen IV,[12] and the α3NC1 domain of collagen IV.[11,13] In contrast, most of the gene product inhibitors have pleiotropic effects that are not necessarily related to the regulation of angiogenesis. For example, thrombospondin-1 and pigment epithelium–derived factor (PEDF), which are well-described inhibitors of angiogenesis in both physiologic and pathologic conditions, can promote endothelial cell apoptosis by inducing the Fas ligand.[14] PEDF originally was isolated as a protein secreted by cultured pigment epithelial cells of fetal human retina,[15] but later was shown to possess plural effects, including neuronal cell differentiation, protection of neurons from various neurotoxic agents, and, most importantly, angiogenesis inhibition.[16] Moreover, in retinal endothelial cells PEDF down-regulates the levels of VEGF, thus preventing vascular permeability and angiogenesis.[17] Finally, there are 2 inhibitors, soluble VEGF receptor 1 and vasohibin, which are expressed only in endothelial cells, and have selective activities against endothelial cells themselves.[11] Soluble VEGF receptor 1 selectively blocks VEGF signaling and only inhibits VEGF-mediated effects, including angiogenesis and vascular permeability. Vasohibin is proposed to be the first negative feedback regulator of angiogenesis and it works by interacting with specific endothelial cell intracellular signaling pathways.

Fig. 1 summarizes the major pro-angiogenic and anti-angiogenic factors that contribute to the homeostasis of blood vessel formation.

DIABETIC NEPHROPATHY AND VASCULAR DAMAGE

The clinical entity of diabetic nephropathy, the most common cause of end-stage renal disease in the developed world, is characterized ini-