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PERSPECTIVES IN BASIC SCIENCE

The role of vascular endothelial growth factor (VEGF) in renal pathophysiology

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The role of vascular endothelial growth factor (VEGF) in renal pathophysiology. Vascular endothelial growth factor (VEGF) is an endothelial-specific growth factor that promotes endothelial cell proliferation, differentiation and survival, mediates endothelium-dependent vasodilatation, induces microvascular hyperpermeability and participates in interstitial matrix remodeling. In the kidney, VEGF expression is most prominent in glomerular podocytes and in tubular epithelial cells, while VEGF receptors are mainly found on preglomerular, glomerular, and peritubular endothelial cells. The role of VEGF in normal renal physiology is essentially unknown. The absence of prominent effects of VEGF blockade in normal experimental animals suggests a limited function during homeostasis, although a role in the formation and maintenance of glomerular capillary endothelial fenestrations has been suggested. VEGF and its receptors are up-regulated in experimental animals and humans with type 1 and type 2 diabetes. Inhibition of VEGF has beneficial effects on diabetes-induced functional and structural alterations, suggesting a deleterious role for VEGF in the pathophysiology of diabetic nephropathy. VEGF is required for glomerular and tubular hypertrophy and proliferation in response to nephron reduction, and loss of VEGF is associated with the development of glomerulosclerosis and tubulointerstitial fibrosis in the remnant kidney. No firm conclusions on the role of VEGF in minimal change or membranous glomerulonephritis can be drawn. VEGF may be an essential mediator of glomerular recovery in proliferative glomerulonephritis. Glomerular and tubulointerstitial repair in thrombotic microangiopathy and cyclosporin nephrotoxicity may also be VEGF-dependent. In conclusion, VEGF is required for growth and proliferation of glomerular and peritubular endothelial cells. While deleterious in some, it may contribute to recovery in other forms of renal diseases.

Key words: compensatory hypertrophy, diabetic nephropathy, glomerulonephritis, transplant rejection, vascular endothelial growth factor (VEGF), uremia.

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Vascular endothelial growth factor (VEGF-A or VEGF), formerly called vasculotropin or vascular permeability factor (VPF), belongs to a family of multipotent cytokines, also including VEGF-B, -C, -D, -E, and placenta growth factor [1]. Alternative exon splicing of a single VEGF gene results in at least six different isoforms. They are homodimeric glycoproteins of 121, 145, 165, 183, 189, and 206 amino acids ($VEGF_{121-206}$) in humans and are one amino acid shorter in rodents [2]. $VEGF_{121}$, $VEGF_{165}$, and $VEGF_{189}$ are the most abundantly expressed isoforms, whereas $VEGF_{145}$ and $VEGF_{206}$ are comparatively rare [2]. VEGF stimulates endothelial cell proliferation and differentiation, increases vascular permeability, mediates endothelium-dependent vasodilatation, and supports vascular survival by preventing endothelial apoptosis [1, 2]. In addition, VEGF induces plasminogen activator, plasminogen activator inhibitor-1 and interstitial collagenase, factors important in matrix remodeling. Furthermore, VEGF promotes monocyte chemotaxis and expression of adhesion molecules [1, 2]. $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{121}$ differ in affinity for heparin and heparan-sulfate proteoglycans ($VEGF_{189} > VEGF_{165} > VEGF_{121}$) and in mitogenic effect ($VEGF_{165} > VEGF_{121}$) [2]. $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$ are in most part sequestered in the extracellular matrix and at the cell surface, whereas $VEGF_{121}$ and $VEGF_{145}$ are freely released [2]. The receptors for VEGF, previously described as fms-like tyrosine kinase (Flt-1) and fetal liver kinase 1 (Flk-1/KDR), now designated as VEGFR-1 and VEGFR-2, respectively, are high-affinity transmembrane tyrosine kinase receptors [2]. Soluble VEGFR-1 (sVEGFR-1), a splice variant of VEGFR-1, regulates VEGF availability by binding VEGF in the circulation [3, 4]. Neuropilin-1 and Neuropilin-2 act as isoform specific co-receptors for VEGF [5]. Hypoxia is the main stimulus for VEGF expression and/or production. Several growth factors and cytokines such as epidermal growth factor, transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor I (IGF-I), angiotensin II, interleukin-1

(IL-1), and IL-6 also have the potential to up-regulate VEGF expression. VEGF may be induced by other factors as well [i.e., prostaglandins, mechanical stress, hyperglycemia, advanced glycation end products (AGEs), protein kinase C (PKC), and reactive oxygen species (ROS)]. VEGF up-regulates the expression of endothelial nitric oxide synthase (NOS3) in endothelial cells and increases the production of nitric oxide [6]. Several lines of evidence have indicated that VEGF exerts its biologic effects through nitric oxide [7]. Nitric oxide may down-regulate VEGF expression and thus function in a negative feedback regulator mechanism [8]. Recently, 15 different sequence polymorphisms have been identified within the VEGF gene, including a C/T base change at position −460, a G/C change at +405 and a A/C change at −141 [9]. The −460C/+405G and −460T/+405C haplotypes are the most frequently observed in the normal population [9]. A correlation of the +405 genotype with production of VEGF has been demonstrated in vitro [9] and in vivo [10], with the highest VEGF production for the GG genotype, intermediate production for the GC genotype and lowest production for the CC genotype [9]. Further, the combination of the +405G genotype with other polymorphisms resulted in higher VEGF promotor activity [11]. A deletion/insertion (D/I) polymorphism at the −2549 position of the VEGF promotor region has been linked to increased transcriptional activity [12].

Angiopoietins form another family of endothelial-specific growth factors consisting of angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2), which bind to tyrosine kinase receptors Tie1 and Tie2 [13]. Angiopoietins and VEGF play co-ordinated and complementary roles in vascular homeostasis [13]. Ang-2 stimulates new blood vessel formation in the presence of VEGF, but promotes endothelial apoptosis and vessel regression when VEGF levels are low [14].

VEGF IN RENAL PHYSIOLOGY

This section elaborates on the expression and the potential role of VEGF, angiopoietins, and their receptors in the normal adult kidney. A comprehensive discussion of the role of the VEGF system in renal development is beyond the scope and space limitations of this review and has been published elsewhere [15]. Cultured rat and human mesangial cells express both mRNA of $VEGF_{121}$, $VEGF_{165}$, and $VEGF_{189}$, and VEGF protein [16, 17]. In rodent and human kidneys, VEGF mRNA and/or protein were detected predominantly in glomerular podocytes, distal tubules, and collecting ducts, and to a lesser extent in some proximal tubules [3, 16, 18–23]. The expression of the different VEGF isoforms in normal human glomeruli was complex and variable with substantial inter- and intraindividual variation [3]. Ang-1, but not Ang-2, was identified in adult human glomeruli, particularly in podocytes [24]. VEGFR-1 and VEGFR-2 were detected in cultured rat and human mesangial cells [25–28] and in cultured rat renal tubular epithelial cells [29], but not in cultured primary human podocytes [30]. In contrast, conditionally immortalized human podocytes expressed VEGFR-1, VEGFR-3 and Neuropilin-1 but not VEGFR-2 [31]. Cultured mouse glomerular endothelial cells and transformed tubular epithelial cells expressed Neuropilin-1 and Neuropilin-2 [32]. Neuropilin-1 was also detected in cultured human mesangial cells [25, 27] and in cultured primary human glomerular podocytes [30]. The expression of VEGFR-1, VEGFR-2, sVEGFR-1, and Neuropilin-1 in isolated human glomeruli was also heterogenous [3, 30]. In human kidney, VEGFR-1 and VEGFR-2 were predominantly expressed on preglomerular, glomerular, and peritubular endothelial cells [20, 23, 27, 33]. In rat kidney, VEGFR-2 expression was detected in glomerular and peritubular endothelial cells, in distal convoluted tubules and collecting ducts, and in cortical interstitial fibroblast and medullary interstitial cells, whereas VEGFR-1 was expressed more diffuse in proximal and distal tubules [19, 29]. In human kidney, Neuropilin-1 was detected in glomerular podocytes [30]. Neuropilin-1 and Neuropilin-2 were localized in peritubular capillary endothelial cells in adult mouse and rat kidney [32]. Tie2 was demonstrated in glomerular capillary endothelial cells of human and rat glomeruli and in cultured human microvascular endothelial cells [24]. In summary, in vivo, capillary endothelial cells express VEGFR-1, VEGFR-2, and Tie2, glomerular podocytes express Neuropilin-1 and produce VEGF and Ang-1.

Although the functions of constitutively expressed VEGF and VEGF receptors in the normal kidney are largely unknown, some hypotheses may be derived from the peculiar distribution of the molecule and its receptors in the kidney. VEGF is strongly expressed by visceral epithelial cells while its binding sites are localized on glomerular endothelial cells. If one assumes the existence of a paracrine loop in the glomerulus, VEGF must move in the opposite direction of the glomerular filtrate in order to bind to its receptors. The presence of such complex mechanism suggests that the strategic localization of podocytes is required for the correct sensing and interpretation of the stimulus for VEGF release. VEGF may be involved in the induction and maintenance of the fenestrae in glomerular capillary endothelial cells [37]. Given the role of VEGF in promoting microvascular permeability, it has been speculated that VEGF may regulate glomerular permeability, although it is generally acknowledged that the capillary fenestrations do not represent the ultimate barrier to filtration. Recently, in vitro evidence indicated that VEGF may act as an autocrine factor on calcium homeostasis and cell survival in human podocytes [31]. In contrast to the prominent expression of the VEGF system in the adult kidney, the administration