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Therapeutic Angiogenesis by VEGF Supplementation for Treatment of Renal Disease

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Abstract

Purpose of Review—Vascular endothelial growth factors (VEGFs) influence renal function through angiogenesis, with VEGF-A being the most potent inducer of vascular formation. In the normal glomerulus, tight homeostatic balance is maintained between the levels of VEGF-A isoforms produced by podocyte cells, and the VEGF receptors (VEGFRs) expressed by glomerular endothelial, mesangial, and podocyte cells. Renal disease occurs when this homeostatic balance is lost, manifesting in the abnormal autocrine and paracrine VEGF-A/VEGFR signaling, ultrastructural glomerular and tubular damage, and impaired filtration.

Recent Findings—Preclinical disease models of ischemic renal injury, including acute ischemia/reperfusion, thrombotic microangiopathy, and chronic renovascular disease, treated with exogenous VEGF supplementation demonstrated therapeutic efficacy. These results suggest a therapeutic VEGF-A paracrine effect on endothelial cells in the context of acute or chronic obstructive ischemia. Conversely, renal dysfunction in diabetic nephropathy appears to occur through an upregulated VEGF autocrine effect on podocyte cells, which is exacerbated by hyperglycemia. Therefore, VEGF supplementation therapy may be contraindicated for treatment of diabetic nephropathy, but specific results will depend on dose and on the specific site of VEGF delivery. A drug delivery system that demonstrates cell specificity for glomerular or peritubular capillaries could be employed to restore balance to VEGF-A/VEGFR2 signaling, and by doing so prevent the progression to end stage renal disease (ESRD).

Summary—This review discusses the preclinical data available for VEGF supplementation therapy in models of renal disease.

Keywords

Vascular endothelial growth factor; therapeutic angiogenesis; renal function; kidney disease

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Introduction

Vascular endothelial growth factors (VEGFs) are soluble ligands that meticulously control the formation and differentiation of blood vessels during angiogenesis (1). Of the five highly conserved members of the VEGF superfamily, VEGF-A is the most potent inducer of angiogenesis (1). VEGF-A is alternatively spliced into seven proangiogenic and five anti-angiogenic isoforms (2,3). Among these isoforms that serve key roles in renal physiology are the predominant VEGF₁₆₅, VEGF₁₂₁, and VEGF₁₈₉ (4,5). These VEGF-A ligands bind to receptor tyrosine kinase VEGF receptors (VEGFRs) (1,6), with VEGFR2 being intricately associated with vascular endothelial cell function, owing to its autophosphorylation of catalytic tyrosine residues present on its cytoplasmic domain (7,8). Located within the glomerular urinary space are the filtration barrier-regulating podocyte cells, which are the chief sources of glomerular VEGF₁₆₅, VEGF₁₂₁, and VEGF₁₈₉ (4,5). Conversely, the most robust expression of VEGFR2 is exhibited by vascular endothelial cells lining the glomerular capillary lumen (9), while mesangial cells and podocytes express VEGFR2 in lesser densities (10,11). The functional consequences of the juxtaposition of VEGFR2 expressing cells to VEGF-A synthesizing podocyte cells are the autocrine and paracrine effects of VEGF/VEGFR2 signaling (12).

The regulation of glomerular filter integrity by VEGF-A is governed through an autocrine effect on podocytes (13). As well as serving as the major source of renal VEGF-A, podocytes express functional VEGFR2s, particularly on foot processes (12,14). VEGF-A released by podocytes bind to VEGFR2 on foot processes, which induces a conformational change that attenuates interaction of VEGFR2 with nephrin, the fundamental transmembrane protein of the slit diaphragm (12,15). Cytoskeletal alterations that involve nck and actin occur within the podocyte foot process, that result in functional adjustments in the slit diaphragm, glomerular filter integrity (15,16), podocytes calcium homeostasis, and cell survival (17,18). Thus, the renal VEGF-A autocrine effect maintains the integrity of the glomerular filtration barrier by adjusting podocyte structure and function (12,15).

The paracrine effect of renal VEGF-A also preserves glomerular filtration barrier integrity, but its focus is on the vascular endothelial cells lining the capillary lumen (19,20). Vascular endothelial cells express the most robust levels of VEGFR2 within the glomerulus (19,21). VEGF-A released from podocytes travels against the ultrafiltration gradient (from urinary space to capillary lumen) to bind to VEGFR2 expressed on glomerular endothelial cells (19,22,23). Podocyte VEGF-A has been observed to stimulate the formation, maintenance, and repair of capillary fenestrations (17,24), transcellular gaps (17,25), caveolae (17,26), and interendothelial gaps (17,27).

The clinical need to address the autocrine/paracrine effects of glomerular VEGF-A/VEGFR2 signaling is illustrated in the high morbidity and mortality rates in acute kidney injury (28,29), diabetic nephropathy (30,31), and chronic kidney disease/ESRD (32). This review discusses the preclinical data available for VEGF supplementation therapy in models of these renal diseases.

VEGF Supplementation for Treatment of Ischemic Renal Injury

VEGF supplementation has shown promise for improving renal function in various models of ischemic renal disease. Reports have demonstrated that VEGF₁₂₁ treatment protected rats from widespread necrosis, glomerular injury, and glomerular and tubulointerstitial cell apoptosis in rat models of renal thrombotic microangiopathy (33,34). Similarly, VEGF was protective against cyclosporine and high-salt diet induced nephropathy (35) and in the remnant kidney model of progressive renal failure (36), where it induced glomerular and peritubular capillary endothelial cell proliferation. Basile et al. demonstrated that VEGF levels are reduced in the initial period after ischemia/reperfusion (I/R) in a rat model (37). However, the reduction was temporary, as VEGF mRNA levels returned to baseline 7 days after I/R, and protein levels were partially recovered after 7 days and nearly fully recovered 35 days after I/R injury (37). In a follow-up study by Leonard et al., rats were administered VEGF₁₂₁ at various treatment windows following injury in a rat chronic kidney disease (CKD) model consisting of I/R combined with initiation of a high salt diet 35 days after the I/R event (38). When VEGF was administered early after the initial injury (either on days 0 – 14, days 0 – 35, or days 3 – 35), vascular density was protected, and renal injury was reduced, with the most striking results present in the rats treated on days 0 – 14. However, this protective effect was lost if VEGF was not administered until days 21 – 35 after injury, indicating, at least in the setting of acute I/R, that renoprotection by VEGF supplementation is most effective if VEGF is administered very early following the ischemic event. Interestingly, the authors elucidated a new mechanism for preservation of renal function by VEGF supplementation. Renoprotection was not attributed to prevention of endothelial cell apoptosis or induction of endothelial cell proliferation by VEGF, but rather to prevention of post-injury endothelial to mesenchymal transition in the peritubular capillaries (39). In contrast, VEGF supplementation was not protective in a renal injury model induced by angiotensin II infusion followed by high salt diet (40). This could be due to the fact that VEGF was not administered during the initial Ang II infusion hypertensive insult, consistent with the results of Leonard (38), or due to the fact that Ang II actually induced VEGF expression (40), indicating a different mechanism for renal pathology in this model.

In a series of studies using a swine model of renal artery stenosis (41–43), Chade et al. have implicated VEGF deficiency and resulting microvascular loss in the deterioration of renal function. Renal artery stenosis induced by placement of a local irritant coil lead to progressive deterioration of renal function over the course of several weeks that was accompanied by reduced renal VEGF expression (43). Administration of VEGF by direct intrarenal injection at the time of induction of the stenosis lead to improved renal function six weeks later. The improved renal function was accompanied by increased microvascular density in vessels up to 80 µm diameter as assessed by *ex vivo* whole-kidney µCT and increased glomerular and peritubular vascular density as assessed by renal histology, presumably by protection of the existing vasculature by VEGF (44). Interestingly, a similar beneficial effect of intrarenal VEGF administration was seen in a follow-up study in which VEGF was administered six weeks after the induction of renal artery stenosis (44). Again, intrarenal VEGF lead to an increase in microvascular density and improved renal function. Importantly, in this model, renal disease was already established at the time of VEGF administration, and these results suggest that VEGF infusion can not only preserve existing

renal vasculature, but it can also reverse chronic hypoxia-induced renal damage. This contrasts with the AKI model in which VEGF was only effective when administered immediately after injury, and this difference may reflect disparities between the pathologies of acute ischemia and reperfusion in the rodent model versus the chronic, progressive loss of renal artery perfusion present in the swine renal artery stenosis model. Similarly, intrarenal VEGF infusion also improved renal function following percutaneous transluminal renal angioplasty relative to stent placement alone (45). Recently, our lab has developed a biopolymer-stabilized form of VEGF by fusing VEGF₁₂₁ to the engineered protein biopolymer elastin-like polypeptide (ELP). Fusion of VEGF to ELP stabilizes the growth factor and slows its plasma clearance (46). In collaboration with Dr. Chade, we tested the ELP-VEGF fusion protein's ability to reverse vascular damage and improve renal function in the swine RVD model. We found that when administered intrarenally six weeks after induction of renal artery stenosis, ELP-VEGF was mostly retained in the injected kidney with some spillover into the contralateral kidney, and it significantly improved renal function and increased microvascular density in the stenotic kidney (47). Importantly, ELP-VEGF outperformed free VEGF in its ability to induce improved renal function, indicating that fusion to the stabilizing biopolymer is beneficial.

Role of VEGF in Diabetic Nephropathy

Diabetic nephropathy (DN) is the primary cause of ESRD worldwide (32) and is characterized by extensive changes within the glomerulus that have been demonstrably linked to VEGF expression and pathways under its direct influence. In contrast to cases of AKI, I/R injury and renal artery stenosis, where VEGF deficiency suggests a diminished paracrine effect in VEGF-A/VEGFR2 signaling, DN is characterized by an augmented autocrine effect on podocyte cells (15,16,22,48,49). Podocytes express insulin receptors, which when activated, trigger the production of VEGF-A in a nephrin-dependent manner (50,51). Furthermore, in the presence of hyperglycemia, mesangial cells express renin and angiotensinogen (52) that stimulates increased production of TGF- β and VEGF-A in podocytes, resulting in augmented thickening of the extracellular matrix and higher rates of podocyte apoptosis (53–55). Clinical cases of DN carry the risk of collapsing glomerulopathy, which is characterized by expansion of the glomerular basement membrane, capillary wall deformation, and epithelial cell proliferation, all of which are associated with an overexpression of glomerular VEGF-A (56–58). Collectively, the progressive changes of DN include increased proteinuria, the fusion of podocyte foot processes, and alterations in glomerular endothelial cell proliferation and maintenance that have all been identified both in humans and multiple animal models (59).

During the early stages of DN, VEGF-A levels have been shown to be markedly increased, and multiple methods which resulted in lower VEGF-A activity during this period have improved DN progression drastically (60–62). Recent work has further described the role of VEGF-mediated pathways in DN, and have identified new potential therapies. In a study of type-1 diabetes via streptozotocin injection in mice, Sivaskandarajah et. al. characterized the glomerular effects VEGF-A knockout in podocytes at either 3–4 weeks (early) or 7–8 weeks (late) post injection (63). Their results clearly show damage from both total VEGF-A KO and/or diabetes compared to controls during both time points, but some results including

total glomerular expansion only reached significance in the late time points. They suggest that increased VEGF-A during early stages of DN may be a compensatory mechanism that could protect renal function. This study could be considered at odds with the results from Oltean et. al. who examined the effects of the anti-angiogenic factor VEGF-A_{165b} in multiple models of DN (64). They found that either podocyte specific overexpression or systemic injection improved multiple indicators of renal health and function including decreased proteinuria and a restoration of the endothelial glycocalyx in multiple animal models as well as human diabetic glomeruli. VEGF-A_{165b} functions on the VEGF receptor 2 and inhibits the angiogenic actions of VEGF-A, suggesting the proangiogenic actions of VEGF-A are not likely primarily a compensatory mechanism in DN (64).

Some models have identified positive feedback loops involving both the ROS-NOS-VEGF pathway as well as the TGF β -CTGF-VEGF pathway, both of which could increase VEGF-A production which further dysregulates the system in DN (54). Multiple studies further support these pathways as contributing factors to the pathophysiology. Jha et. al. (61) induced a Nox4 deletion in the podocytes in a streptozotocin-induced diabetes model and found significant renoprotection and decreases in renal VEGF-A levels. Likewise, Hou et. al. (65) identified renoprotective effects and decreased VEGF expression related to an improved uncoupling of the VEGF - NO axis within the glomerulus via adiponectin administration. In DN, the increase in VEGF-A occurs with a lower eNOS activity, resulting in a decoupling of VEGF-A and nitric oxide (66,67). In a similar streptozotocin model, the administration of progesterone to ovariectomized rats resulted in significantly improved renal function that was associated with marked decreases in TGF β , CTGF, and VEGF mRNA levels as well as increased mRNA levels of podocin and nephrin (68). Given these results and the commonality of VEGF to both of these pathways, VEGF and VEGF-R2 are further supported as potential therapeutic targets, and given that both heightened expression or knockout lead to increased glomerular dysfunction in DN, it is likely that maintenance of VEGF-A activity levels within the normal range during disease onset could prove an effective therapeutic option (54,65).

Conclusion

It is evident from the studies discussed above that there is an intriguing link between VEGF signaling and the maintenance of renal vascular and glomerular health. There remains, however a number of unresolved biological mechanisms linking the two, and further mechanistic studies are warranted. In the cases of thrombotic microangiopathy, ischemia reperfusion, and chronic renovascular disease, the vast majority of the published evidence suggests a protective effect of VEGF supplementation. However, timing of the intervention may be critical, and efforts to intervene with therapeutic angiogenesis early in the disease course may be most effective. In diabetic nephropathy, the literature are more conflicting, and the benefit of VEGF supplementation therapy is less clear. In the case of diabetic nephropathy, it may be critical to carefully dose VEGF augmentation therapy (either supplementation or inhibition) to restore VEGF levels to their normal physiological state. However, this will be difficult to achieve in practice, especially given the wide spectrum of disease severity at clinical diagnosis. Therefore, an alternative strategy could be to target VEGF supplementation therapy to the vascular endothelium and prevent podocyte exposure

using cell-specific or large size, unfiltered, drug delivery systems. Current work in our lab involves the development of just such a system using the ELP biopolymer, whose size is easily modified to modulate its permeability to the filtration barrier and whose sequence is easily modified to add cell-type targeting agents. In summary, in both the cases of obstructive ischemic injury and diabetic induced nephropathy, the preponderance of existing evidence suggests that VEGF administration can be beneficial in the protection of the glomerular ultrastructure and the renal vasculature. There do remain, however, some uncertainties about the best timing, duration, and dosing of VEGF that are most beneficial in each disease state. Further studies are warranted to address these points, as well as improving route of administration, formulation, and drug delivery to optimize appropriate renal dosing and intrarenal localization without inducing adverse effects on the filtration barrier.

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Key Points

- Locally produced VEGF-A family members are crucial for maintenance of glomerular health.
- VEGF production is altered in response to renal ischemia, and exogenous administration of VEGF has been shown to be renoprotective, particularly when administered near the time of injury.
- There is a potential use of VEGF for treatment of diabetic nephropathy, however, VEGF excess can also potentiate disease progression; suggesting a narrower therapeutic window.
- A drug delivery system capable of modulating the VEGF delivery specifically to glomerular and peritubular vascular endothelial cells is a potentially powerful tool for renal therapeutic angiogenesis.