

The Effectiveness of VEGF Signalling Pathway Inhibitors on the Kidney and Their Immunoregulation Mechanism

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Abstract

Pathophysiologic processes that are closely related are angiogenesis and immunosuppression. VEGF signaling pathway inhibitors, which are frequently prescribed for proliferative retinal lesions and malignant tumors, can induce hypertension and renal damage in certain patients. These patients may present with proteinuria, nephrotic syndrome, renal failure, and thrombotic microangiopathy. VEGF-A and VEGF-C are both inhibited by VEGF signaling pathway inhibitors. Nonetheless, glomerular endothelial cells' and podocytes' physiological function depends on the VEGF-A and VEGF-C that podocytes produce. For kidney disease linked to inhibitors of the VEGF signaling pathway, there is currently no proven treatment, and some patients continue to experience progressive renal failure even after stopping their medication. According to recent research, VEGF-A and VEGF-C blocking can increase cytotoxicity of CD4 + and CD8 + T cells, strengthen dendritic cells' ability to present antigens, and activate CD4 + and CD8+ T cells.

Keywords: Immunoregulation; Microangiopathy; signalling pathway; VEGF-C; Proteinuria; CD4+.

Introduction

One important angiogenesis factor, vascular endothelial growth factor (VEGF), suppresses the immune system in the context of anti-tumor immunity. Two groups of VEGF signaling pathway inhibitors are distinguished: Bevacizumab, ranibizumab, aflibercept, and ramucirumab are examples of drugs that directly inhibit VEGF-A through antibody binding or VEGF trapping; tyrosine kinase inhibitors, such as sunitinib, pazopanib, sorafenib, cabozantinib, vandetanib, motesanib, cediranib, axitinib, regorafenib, tivozanib, linifanib, dasatinib, imatinib, and quizartinib. Bevacizumab therapy maintains VEGFR2 activation through a compensatory increase in VEGF-C. Both VEGF-A and VEGF-C can be inhibited by tyrosine kinase inhibitors of VEGF signaling.1-2 Nonetheless, glomerular endothelial cells' and podocytes' physiological function depends on the VEGF-A and VEGF-C that podocytes produce. Similarly, when used in malignant tumors, VEGF signaling pathway inhibitors result in adverse events related to the kidneys [1,2].

Methodology

By boosting the quantity of tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T (Treg) cells as well as their immunosuppressive capabilities, VEGF-A produces a pro-tumor microenvironment. Chronic VEGF exposure (as seen in cancer patients and animals containing tumors) will eventually cause immune function to decline since the thymus is unable to produce new peripheral T cells.17. Treatment of non-tumor-bearing mice with a continuous infusion of recombinant VEGF will result in defects in the DC, a reduction in T cell counts, and a decrease in the ratio of T cells to B cells in the spleen and lymph nodes. It has been proposed that VEGF plays a role in the myeloid, lymphoid, and monocyte/macrophage lineages' immunosuppressive mechanisms. As a result, inhibitors of the VEGF signaling pathway both destroy the tumor microenvironment and stimulate the immune system [3].

Accordingly, immunological cell activation may contribute to the pathophysiology of kidney disease linked to inhibitors of the VEGF signaling pathway. The expression and roles of VEGF-A and VEGF-C in the kidney are outlined in this review. We review the current

immunoregulation mechanisms of inhibitors of the VEGF signaling pathway. In order to emphasize the suggestion for inhibitors of the VEGF signaling pathway, combine strategies are finally summarized.

The kidney's VEGF-VEGFR pathway: expression and function

The seven subtypes of the VEGF family are placental growth factors 1 and 2, VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E. VEGF-A and VEGF-C are the primary regulators of tubular cells, podocytes, and glomerular capillary endothelial cells. The production of VEGF-A and VEGF-C by podocytes is essential for preserving the normal physiological function of podocytes and glomerular endothelial cells. In mouse podocytes, targeted VEGF gene deletion results in endothelial cell enlargement, collagenous fibrin deposition, red blood cell debris in the glomerular capillary loop cavity, and potentially irreversible thrombotic microangiopathy. The binding of VEGF to VEGF receptor tyrosine kinases (RTK), such as VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), VEGFR-3 (Flt-4) and two coreceptors—NRP (Neuropilin) 1 and NRP2—mediates the physiologic function of VEGF. VEGF receptor 1 (VEGFR1), VEGFR 2, VEGFR 3, and coreceptor-NRP1. It among the VEGF receptors expressed in glomerular capillary endothelial cells and podocytes. The placenta produces soluble Vascular Endothelial Cell Growth Factor Receptor 1, or sVEGFR1, which functions as a decoy receptor to sequester excessive extracellular VEGF-A. This can cause hypertension, endothelial dysfunction, and proteinuria, which are the symptoms of preeclampsia [4,5].

VEGF-A and VEGF-C's function in glomerular disease

The autocrine secreted VEGF-A and VEGF-C are essential for

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the pro-apoptotic p38 MAPK pathway mediated by VEGFR-2 in podocytes to be suppressed and the anti-apoptotic phosphoinositol 3-kinase/AKT pathway to be activated.^{3,24} VEGF-A inhibits podocyte apoptosis by promoting nephrin phosphorylation and enhancing the interaction between podocin and CD2AP. The filtration membrane's three layers are damaged in adult mice lacking VEGF-A. Collapsing glomerulopathy, on the other hand, is another risk factor for renal failure associated with podocyte overexpression of VEGF-A.²⁵ Excessive expression of VEGF-A in diabetes induces the activation of the TGF- β 1 and CTGF signaling pathway, augmenting the proliferation of mesangial and endothelial cells, foot process effacement, and thickening of the glomerular basement membrane. Ultimately leading to renal fibrosis. Consequently, the establishment and maintenance of a normal glomerular filtration membrane depend on tightly regulated VEGF-A. In diabetic kidney disease, VEGF-C lowers endothelial permeability to albumin and increases the fenestra density of glomerular capillary endothelial cells. These actions reduce the level of microalbuminuria.^{6,29} According to recent research; lip toxicity-induced lymphangiogenesis is mediated by VEGF-C/VEGFR3. In diabetic nephropathy, lip toxicity-induced lymphangiogenesis can be reduced, and renal damage can be lessened by inhibiting lymphatic proliferation through the use of a selective VEGFR-3 inhibitor [6,7].

Renal tubulointerstitial disease: The function of VEGF-A and VEGF-C

Inhibitors of the VEGF signaling pathway also cause renal tubular injury. Renal tubular epithelial cells express VEGF-A, with the thick ascending limb of Henle's loop expressing the most of the protein.⁴² Derived from renal tubules Because it promotes tubule-vascular cross-talk with the VEGFR2-expressing peritubular capillaries, VEGF-A is essential for the maintenance of the peritubular microvasculature.⁴³ The process linked to the transition from acute kidney injury to chronic kidney disease is peritubular capillary rarefaction and chronic renal hypoxia, which can be partially caused by a decrease in VEGF-A gene expression or hypermethylation of the VEGF-A promoter gene. Transgenic mice expressing overexpression of VEGF-A in the renal tubules displayed increased growth and formation of tubular epithelial cells and cysts, as well as peritubular capillary proliferation and glomerulomegaly.

Externally generated VEGF-C supplementation has been observed in salt-sensitive hypertensive rat models and unilateral ureteral obstruction (UUO) models to enhance renal lymphangiogenesis and reduce renal fibrosis. In addition to lowering the amount of inflammatory cytokines and oxidative stress products, VEGF-C may also induce the polarization of M2-type macrophages. On the other hand, while chronic disordered lymphatic vessel expansion may impair the ability of activated antigen-presenting cells to efficiently empty the interstitial compartment, which in turn may exacerbate renal fibrosis, it can also stimulate an inflammatory response. Five One In mouse lacking the connective tissue growth factor (CTGF) gene, unilateral ureteral obstruction (UUO) can be induced. This leads to increased VEGF-C expression in renal tubulointerstitial lesions and faster renal fibrosis caused by exogenous CTGF through lymphangiogenesis.

VEGF-A and VEGF-C are generally necessary to preserve the physiological functions of tubular cells, glomerular endothelial cells, and podocytes. Subnormal release of VEGF-A and VEGF-C can cause damage to the tubules and glomeruli. Since VEGF plays a role in the myeloid, lymphoid, and monocyte-macrophage lineages' immunosuppressive mechanisms, inhibitors of the VEGF signaling pathway will correspondingly activate immune cells. Understanding

the immunopathogenesis of kidney disease linked to VEGF pathway inhibitors is aided by reviews concerning the immunoregulation mechanism of the VEGF pathway. Finding a new treatment plan for kidney disease linked to VEGF pathway inhibitors in the interim may be beneficial' [8].

The function of VEGF-A and VEGF-C in T cells

Thymocytes and lymph node cells have been shown in earlier research to constitutively express VEGF-A, VEGF-C, and VEGFRs, such as VEGFR2, VEGFR3, NRP1, and NRP2.⁵³ Activated T cells induce the expression of VEGF and its receptors, such as VEGFR1 and VEGFR2. It has been documented that hematopoietic progenitor cells cannot differentiate into CD8+ and CD4+ T cells when exposed to VEGF-A.⁵⁵ The proliferation and cytotoxic potential of T lymphocytes derived from both healthy individuals and ovarian cancer patients are inhibited by VEGF-A signaling through VEGFR2.⁵³ Additionally, immune tolerance can be induced by VEGF-A via the following mechanisms: T helper type 2 (Th2) polarization is promoted by VEGF-A; (2) VEGF-A.

Contributes to CD8+ T cell exhaustion; (3) VEGF-A increases the expression of immune-checkpoint molecules, such as lymphocyte activation gene 3 protein (LAG3), T cell immunoglobulin mucin receptor 3 (TIM3), and PD-1.^{11, 12, 13, 17, and 1858} Furthermore, significant levels of sVEGFR-1, which is involved in VEGF-A immunoregulation, were also discovered in the supernatants of leukemia cell lines.¹⁵ In allergic airways, VEGF-C/VEGFR-3 activation plays a role in both initiating the acute inflammatory response and regulating the adaptive (memory) response, potentially through modulating the balance between Th2 and Treg cells. In tracheal allografts, overexpression of VEGF-C results in CD4+ T cell infiltration, neutrophil chemotaxis, and a transition toward a Th17 adaptive immune response. This is succeeded by an increase in lymphangiogenesis and the development of obliterative bronchiolitis [9,10].

Results

For glomerulonephritis, anti-platelet aggregation therapy is highly advised. The activation of the complement system has multiple points of contact with activated platelets, which are a crucial mediator between inflammation and microvascular endothelial dysfunction. Additionally, a study found that bevacizumab will bind to VEGF dimer and form large, multimeric complexes that can promote platelet activation and aggregation when its molar concentration is roughly ten times that of VEGF.¹⁰⁹ When anti-VEGF agents were administered to eNOS-deficient mice, the glomeruli showed the deposition of tissue factor and fibrin thrombi.¹⁰¹ Anti-VEGF substances are internalized by alpha-granules, whereupon they may activate platelets and consequently contribute to thromboembolic episodes. Generally speaking, inhibitors of the VEGF signaling pathway, particularly bevacizumab, can stimulate platelet activation, which will increase adhesion to endothelial cells, improve inflammatory cells' chemotaxis, and complement activation, ultimately resulting in microthrombi. Anti-platelet therapy may therefore be advantageous for kidney disease linked to inhibitors of the VEGF signaling pathway.

Discussion

Certain Chinese herbs (*Angelica sinensis* and its ingredient, sodium ferulate, *Poria cocos*) and sulodexide may be useful in lessening the injury of glomerular endothelial cells because VEGF signaling pathway inhibitors cause injury to these cells. In our investigation, we discovered that in bevacizumab-induced endothelial cell injury, pachymaran and *Angelica Polysaccharide* both enhanced the expression of cytoskeleton

proteins, complement H factor, and thrombomodulin.

Conclusion

For podocytes, renal tubular epithelial cells, and glomerular endothelial cells to continue functioning normally, VEGF-A and VEGF-C are essential. The following mechanisms could result in immunopathogenesis in the kidney if the VEGF signaling pathway is blocked: cytotoxic T cell activation; Treg cell reduction; Th1 skewing of immunity and M1 macrophage polarization; promotion of dendritic cell maturation and antigen presentation; and induction of complement cascade activation. Thus, treatment with complement inhibition and immunosuppression is thought to be beneficial in reducing kidney disease linked to inhibitors of the VEGF signaling pathway. Supplementing VEGF to the kidneys may be a promising treatment for kidney disease brought on by VEGF blocking medications. Additionally, anti-platelet therapy and glomerular endothelial injury improvement therapies may be helpful for kidney disease

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