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ANGIOGENIC CYTOKINES IN RENOVASCULAR DISEASE: DO THEY HAVE POTENTIAL FOR THERAPEUTIC USE?

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Abstract

Experimental and clinical studies suggest that the damage of the renal microvascular function and architecture may participate in the early steps of renal injury in chronic renal disease, irrespective of the cause. This supporting evidence has provided the impetus to targeting the renal microvasculature as an attempt to interfere with the progressive nature of the disease process.

Chronic renovascular disease is often associated with renal microvascular dysfunction, damage, loss, and defective renal angiogenesis associated with progressive renal dysfunction and damage. It is possible that damage of the renal microvasculature in renovascular disease constitutes an initiating event for renal injury and contributes towards progressive and later on irreversible renal injury. Recent studies have suggested that protection of the renal microcirculation can slow or halt the progression of renal injury in this disease.

This brief review will focus on the therapeutic potential and feasibility of using angiogenic cytokines to protect the kidney microvasculature in chronic renovascular disease. There is limited but provocative evidence showing that stimulation of vascular proliferation and repair using vascular endothelial growth factor or hepatocyte growth factor can slow the progression of renal damage, stabilize renal function, and protect the renal parenchyma. Such interventions may potentially constitute a sole strategy to preserve renal function and/or a co-adjuvant tool to improve the success of current therapeutic approaches in renovascular disease.

Keywords

kidney; cytokines; angiogenesis; renovascular disease; microcirculation

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Introduction

Patients with chronic kidney disease (CKD) have a 5 fold increase in co-morbid conditions and a 50% higher rate of hospitalization¹. Chronic renovascular disease (RVD) is a progressive disease that currently accounts for up to 16% of all cases of CKD and end stage renal disease^{2, 3}, whose incidence increases with age and represents a major health problem and economical burden for the US and worldwide. The main etiology of RVD is atherosclerotic renal artery stenosis, which could be found in up to 40% of patients older than 65². Patients with RVD show 2 major pathological hallmarks: hypertension and progressive renal dysfunction. A large number of patients with RVD are usually treated using aggressive medical therapy such as renin-angiotensin receptor blockers and statins, among other agents^{4, 5}. Another frequently used approach in these patients is to treat and resolve renal artery stenosis by therapeutic renal angioplasty, usually combined with pre-existent medical therapy. However, the success in recovering renal function or restoring normal blood pressure through medical or interventional approaches is often not achieved⁶. Little progress has been made to improve the relatively poor outcomes of catheter-based interventions in patients with chronic RVD but numerous studies have focused on comparing both strategies (medical therapy vs. renal revascularization) to find an answer. Whether one strategy is better than the other is still not established^{7–10}, and randomized trials or their analysis are still in progress¹¹. Thus, identification of novel therapeutic targets could help to refine current approaches as in turn could modify the progressive nature of renal injury in RVD and contribute to the design of novel therapeutic approaches.

Renal microvascular disease and progression of renal injury in RVD

Microvascular (MV) disease in general is defined by the structural damage, dysfunction, and/or loss of the microvasculature, which is a key contributor to the progression of damage in the tissues^{6, 12–15}. The microcirculation is constituted by those vessels between 0–200 μm in diameter embedded within organs and responsible for the distribution of blood within tissues¹⁶. A progressive renal MV disease¹⁷ has been suggested to play a major pathological role on the poor improvements on renal function after renal angioplasty. The lack of a definitive treatment in patients with RVD has been indeed the incentive for major research efforts in experimental models to identify potential therapeutic approaches^{18–23}. MV disease in the kidney can compromise both the renal nutrition and function and is a prominent pathological feature in CKD that progresses as renal function declines²⁴, irrespective of the etiology. Possibly initiated by augmented vasoconstriction and endothelial dysfunction in CKD²⁵, MV disease can alter renal hemodynamics and function, lead to a progressive decrease in peritubular capillary flow, and consequently result in mild tubulo-interstitial ischemia²⁶, which could constitute both a cause and/or a consequence of progressive renal damage.

Angiogenic cytokines: a potential renoprotective intervention in RVD?

The defined actions of angiogenic cytokines have been the engine for numerous studies in other fields such as cancer, in which inhibition of angiogenesis plays a central role for tumor development and expansion of the disease. For example, anti-VEGF therapies are part of the first line of treatment in colon cancer²⁷ and the potential application of such strategies in other type of solid tumors is under investigation^{28, 29}. However, the arresting of pathological vascular proliferation carries some severe adverse effects on the cardiovascular and renal system mainly due to hypertension and renal damage, which seems to be triggered partly by a collateral but significant MV damage in the renal parenchyma³⁰. These concepts are further supported by previous studies showing that down-regulation of the VEGF pathway

in normal organs can also lead to MV disturbances and even regression of blood vessels, which could be worsened by concurrent pathological conditions³¹.

On the other hand, previous studies have shown that the defective intra-renal vasculature frequently observed in CKD is usually associated with a significant decrease in circulating^{24, 32, 33} and renal^{18–21} angiogenic cytokines. This stage of MV damage seems to be provoked by a marked imbalance between factors that participate in the tight regulation of vascular homeostasis. The decrease in these factors may certainly play a role not only in inducing MV dysfunction, but also in blunting renal MV repair and promoting progressive MV damage and loss.

Therapeutic angiogenesis is a promising strategy that has been shown to be feasible and effective in treatment of peripheral vascular disease and mainly, chronic limb ischemia. The basic principle is the stimulation of neovessel formation to recuperate adequate blood supply needed to sustain tissue function. The purpose of this mini-review is to discuss the potential use of angiogenic cytokines (following the same principle) to protect the kidney in RVD, based on promising clinical and experimental evidence on the kidney and other organs. The use of angiogenic cytokines offers, in general, a safe therapeutic alternative either by local administration of pro-angiogenic factors (as recombinant proteins) or by gene therapy. However, most of these interventions are still in a pre-clinical phase. Moreover, their potential application for chronic renal disease is still in early experimental but promising stages. In the next sections, we will focus on experimental and clinical evidence showing potential therapeutic uses for angiogenic cytokines for the kidney. A brief but representative summary of studies using angiogenic cytokines in the kidney and other ischemic territories (and outcomes) is depicted in Table 1. For an in depth review on the biology of the specific factors discussed the reader will be referred to seminal papers and reviews.

Vascular endothelial growth factor (VEGF)

VEGF is a pivotal angiogenic and pro-survival factor that operates in concert with other factors to promote cell division, migration of endothelial of cell progenitors^{34, 35}, endothelial cell survival, and vascular proliferation during developmental phases and in tissues facing an ischemic insult. These processes dynamically generate, repair, and maintain MV networks everywhere, including those in the kidney. Vascular endothelial growth factor plays a critical role in glomerular development and function³⁶, and inhibition of VEGF (a frequent therapeutic approach in cancer) is associated with hypertension and renal injury³⁰. The focus of this section is the angiogenic effects of VEGF and its potential application as a renal therapeutic intervention. Since the review of the biology of VEGF is beyond the scope of this section, the reader is suggested to consult previously published work^{36, 37}.

Therapeutic use of VEGF: clinical and experimental evidence

The administration of exogenous VEGF has been used in clinical and experimental settings and showed protective actions on MV function and architecture in different pathological milieus, such as the ischemic myocardium^{38, 39} and hind-limb⁴⁰. Furthermore, recent work in rodents^{41–43} has shown the importance of renal VEGF for the progression of renal injury and supported the feasibility of using VEGF therapy. Using a swine model of chronic renal artery stenosis as a surrogate of RVD, our previous studies have demonstrated that a progressive MV loss in the stenotic kidney correlates with progressive renal damage. We have also shown that renal VEGF progressively decrease in the kidney, which in turn correlates with the evolving deterioration of renal function and MV rarefaction in the stenotic kidney^{19–21, 44}. These seminal findings support a central role for VEGF on the progression of renal injury in RVD and gave us the rationale for using exogenous VEGF as a therapeutic tool to protect the kidney.

The renal replenishment of VEGF showed renoprotective actions in RVD, both as a preventive (when administered at the onset of RVD) and as a therapeutic intervention at a later stage of the disease^{18, 20, 44}. Intra-renal VEGF improved renal function and restores MV density by stimulating MV proliferation in the stenotic kidney, underscoring the importance of renal MV integrity for renal function. The infusion of this cytokine with a short half-life seems to induce a powerful stimulus on the angiogenic cascade, since a single intra-renal administration in the stenotic kidney augmented the glomerular and tubular expression of VEGF and of key mediators of its actions^{18, 20, 44}. VEGF-therapy increased renal Akt, a key pro-survival factor, and Ang-1/Tie-2²⁰, which together with VEGF and Akt⁴⁵ can stimulate the recruitment and homing of cell progenitors into ischemic tissues to promote neovascularization⁴⁶, maturation of the newly generated vessels, and repair of damaged pre-existing ones^{47, 48}. Another pivotal mediator of VEGF is endothelial nitric oxide synthase (eNOS). Increased renal eNOS after administration of VEGF may suggest augmented NO bio-availability²⁰, which plays an important role in VEGF-induced MV sprouting⁴⁹ and enhances protection of tubular and glomerular cells from injury⁵⁰. These studies support the feasibility of VEGF therapy as a potential tool for treatment of the ischemic kidney (Figure 1). The restoration of the renal angiogenic cascade and subsequent protection of the renal microcirculation in the stenotic kidney^{18, 20} was functionally consequential since it recovered renal function, decreased renal fibrosis, and even improved responses to renal angioplasty^{20, 44}.

Hepatocyte growth factor (HGF)

Hepatocyte growth factor (HGF) is a pleiotropic mesenchymal growth factor that plays a pivotal role in renal tubular repair and regeneration. HGF elicits potent mitogenic, anti-fibrotic, anti-inflammatory, and pro-survival activities mainly in renal tubular epithelial and in endothelial cells. HGF constitute a paired signaling system with its specific receptor c-Met, participating in renal development and the maintenance of normal adult kidney structure and functions. The readers are invited to consult published work to revise in depth the biology of HGF and additional actions in the kidney^{51–54}.

Therapeutic use of HGF: experimental and clinical evidence

Tissue ischemia is a potent stimulus for generation and release of HGF, and previous studies have shown HGF to increase in myocardial⁵⁵ and cerebral⁵⁶ ischemia and peripheral vascular disease⁵⁷, indicating that this growth factor is ubiquitous. HGF has been indicated as a powerful vasculo-protective factor by promoting MV repair and MV proliferation. The effects on the vasculature are achieved both directly and by synergistic interactions with other prominent angiogenic factors such as VEGF and angiopoietins⁴⁶, supporting a central role of this pleiotropic growth factor. The vasculogenic effects of HGF have been recently shown in the ischemic myocardium of a swine model after a single intra-coronary dose⁵⁸, underscoring powerful and long-lasting effects possibly mediated via enhanced activation and mobilization of cell progenitors.

Pioneering work from Gong et al have also shown that HGF is a pivotal factor in mediating renal damage and could serve as a potential therapeutic target for renoprotection^{53, 54}. Indeed, these elegant studies showed that targeting HGF (both stimulation and blockade) led to changes in the development and resolution of renal inflammation^{53, 54} by down-regulation of specific downstream mediators such as monocyte-chemoattractant protein (MCP)-1 and nuclear factor kappa (NFκ)-B both at tubular and endothelial cell level. Furthermore, other studies have shown that HGF is a powerful antagonist of TGF-β and a down-regulator of the TGF-β/Smad pathway, a central player in mediating renal fibrosis⁵². Thus, this experimental pre-clinical evidence supports a role for HGF in preserving the kidney beyond its angiogenic and vasculo-protective effects. In addition to the anti-inflammatory and anti-fibrotic actions,

our previous studies using a swine model of chronic RVD have shown that up-regulation of HGF in the stenotic kidney is indeed renoprotective. Augmented expression of renal HGF (secondary to chronic endothelin blockade⁵⁹ or statins²³) was associated to significant improvements in renal hemodynamics and a substantial decrease in renal injury. Moreover, we have also recently shown that an intra-renal administration of HGF into the stenotic kidney at an advance stage of RVD and established renal injury induced a significant reduction in renal inflammation, apoptosis, fibrosis and MV remodeling⁶⁰ (Figure 2).

The clinical evidence supporting a therapeutic use of HGF is still limited but promising, although none of these studies were on renal disease. Recent studies using HGF gene therapy (plasmidial constructs) in a relatively small number of patients with critical limb ischemia showed that this approach was safe and effective in reducing symptoms (pain at rest) and the rate of major amputations^{61, 62}. Furthermore, in a recent phase I/IIa study, the safety and potential efficacy of intramuscular injection of plasmid HGF in patients with critical limb ischemia was investigated, and no serious adverse events were noted but significant clinical improvement observed after 6 months⁶³. Overall, the pre-clinical and clinical evidence supports promising effects and potential use for HGF therapy. Nevertheless, additional studies are needed to determine the efficacy, safety profile, and application of HGF in other ischemic tissues.

Potential use of other angiogenic cytokines: evidence on the kidney and other organs

In general, the supporting evidence of using angiogenic cytokines as a therapeutic tool in the kidney is scant and mainly includes the use of HGF or VEGF. In the next sections, we will discuss other angiogenic factors that could potentially be considered for renal tissue protection and may offer alternative strategies for renovascular disease. However, their feasibility as renal therapeutic interventions needs to be addressed in future studies.

Fibroblast growth factor (FGF)

This growth factor is capable of inducing angiogenesis by stimulating proliferation, migration, and differentiation of endothelial cells. FGF-1 and -2 are the most studied and have been used in gene therapy trials of chronic limb ischemia. On the positive side, the intra-muscular administration of this factor has shown to be free of adverse events. However, despite some evidence suggestive of reductions in the need of limb amputation and reductions of symptoms, the results of these multi-centric phase II trials^{64–66} are still not conclusive and further studies are needed before translation into clinical practice.

In the kidney, FGF is constitutively expressed in tubules, plays an important role during kidney development and differentiation, and it has been suggested to play a role in tubular regeneration after injury^{67–69}. Only few studies have focused on the role of FGF in renal ischemia, and results are controversial. A recent study using transgenic mice expressing FGF-1 in endothelial cells suggests that FGF may also interfere with kidney repair after ischemic injury⁷⁰. On the other hand, other studies suggest that inhibition of FGF receptors may indeed exacerbate kidney damage and blunts repair after acute renal ischemia^{71, 72}. There are no studies investigating the role of FGF therapy in chronic renal disease. Thus, the potential for using this growth factor in RVD is still unexplored.

Hypoxia induced (HIF)-1 α

This transcriptional regulatory factor plays a principal role in coordinating adaptive responses to hypoxia and a central regulator of oxygen homeostasis and metabolism at the

cellular level. HIF-1 α interacts and promotes the generation and release of VEGF, angiopoietins, endothelial nitric oxide synthase and other key factors for MV proliferation and development. These clear-cut effects and interactions of HIF-1 α had made it an attractive tool for therapeutic interventions. Experimental studies in rabbit and rodent models of limb ischemia showed that HIF-1 α therapy increased regional blood flow and tissue perfusion via augmented proliferation of capillaries and collateral vessels^{73, 74}. The promising pre-clinical results were the impetus for application of this therapy in humans. Although the use of intra-muscular HIF-1 α gene therapy in patients with symptomatic peripheral vascular disease was safe, the results showed that the administration of local HIF-1 α therapy did not result in any beneficial effect or stimulation of downstream pathways of HIF-1 α ⁷⁵.

There are few data to support the use of HIF-1 α therapy in the kidney. We have shown that renal HIF-1 α progressively decreases in the stenotic kidney of the swine model of chronic RVD²¹. This decrease is accompanied by blunted expression of other angiogenic factors such as VEGF and angiopoietins, and followed by a progressive renal MV rarefaction, deterioration of renal function, and fibrosis. Whether HIF-1 α therapy may serve as a therapeutic intervention in the kidney with defective MV function and/or architecture remains to be investigated.

Platelet-derived growth factor (PDGF)

PDGF belongs to a superfamily of growth factors and is structurally and functionally related to other growth factors such as VEGF. This ubiquitous growth factor plays crucial roles during development of the glomerular endothelium and mesangium^{76, 77}, but there is limited evidence for normal physiological functions in the adult. However, increased PDGF activity has been observed in several diseases and pathological conditions such as atherosclerosis, neurological disorders, and chronic renal disease^{78, 79}. Indeed, numerous reports show that increased PDGF accompanies renal inflammation⁸⁰ and the development and progression of renal fibrosis^{81–83}, suggesting a pathological role of this factor. Despite the role of PDGF in renal microvascular development and expansion⁷⁷, its role as a pro-fibrotic agent (mainly directly⁸⁴, but also by interactions with transforming-growth factor- β ⁸⁵) has been the impetus for studies attempting to block PDGF in renal disease⁸⁶ and only a few have attempted PDGF stimulation for therapeutic purposes⁸⁷.

A word of caution

Although the renal administration of angiogenic cytokines such as VEGF or HGF have suggested promising effects (at least on experimental settings) a number of potential adverse or collateral effects that could unravel by using pro-angiogenic strategies should be kept in mind. Hypotension³⁹ or generation of highly permeable and poorly functional vessels^{88, 89} may occur and facilitate renal injury by, for example, allowing the leakage of injurious cytokines to the extra-vascular space should the latter occurs. Furthermore, pro-angiogenic factors are central for tumor development. Therefore, these potential scenarios warrant a cautious approach for these therapeutic strategies to be used in RVD. Furthermore, it emphasizes that careful selection and follow-up of the patients to avoid undesired effects is crucial should administration of angiogenic cytokines move forward into clinical trials.

Conclusion and Perspectives

The underestimation of MV disease could be a major player in defining the outcomes of renal angioplasty as well as the progression of renal injury in renal artery stenosis and RVD. The severity of renal parenchymal damage may define the turning point towards irreversible renal injury, which may consequently compromise the chances to successfully recover renal

function and improve blood pressure control after renal angioplasty. Accurate clinically available high-resolution imaging tools and techniques to assess MV distribution and evaluation of MV function (e.g.: ultrasound, CT imaging) could serve as means to better determine the severity of renal MV disease and damage. The targeted use of some angiogenic cytokines has shown promising renoprotective effects in clinically relevant experimental settings^{41, 4318, 20, 44} indicating that pro-angiogenic interventions could induce a significant renoprotection. However, it should be emphasized that these studies were still experimental and in single-disease models, and humans with RVD often have several comorbid conditions such as long-term hypertension, lipid abnormalities, or diabetes that add challenges to therapeutic strategies. Nevertheless, those studies offer new potential therapeutic alternatives for the design of prospective experimental and clinical studies. Further research is needed to determine their optimal therapeutic use, both as a stand-alone treatment or, possibly, as a co-adjuvant intervention that could offer new therapeutic options for the treatment of patients with RVD.

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Figure 1.

a) Schematic illustration and micro-CT reconstruction of the renal microcirculation in the stenotic kidney describing the general process of the deterioration of renal function and microvascular (MV) rarefaction and their consequences. b) Schematic illustration and micro-CT reconstruction of the renal microcirculation in the stenotic kidney after intra-renal administration of VEGF, describing the potential mechanisms of VEGF-induced MV and renal protection.

CT: computer tomography; VEGF: vascular endothelial growth factor; RBF: renal blood flow; GFR: glomerular filtration rate; NO: nitric oxide; Angio: angiopoietins; EPC: endothelial progenitor cells.

Figure 2.

Schematic flowchart describing the potential underlying mechanisms of HGF-induced renoprotection. HGF is a powerful anti-inflammatory, anti-fibrotic, and pro-angiogenic factor that could exert its effects directly and by interaction with other cytokines. HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor; TGF- β : transforming growth factor- β ; MCP-1: monocyte-chemoattractant protein-1; NF κ B: nuclear factor kappa-B; MV: microvascular, ECM: extracellular matrix.

Table 1

Examples of studies using angiogenic cytokines therapeutically

Growth Factors	Clinical/Experimental	Goals	Outcome
VEGF-121 ⁴³	Experimental	VEGF to preserve vascular structure and renal function after ischemia.	VEGF treatment attenuated renal MV rarefaction and cell death.
VEGF-121 ⁹⁰	Experimental	VEGF therapy to enhance recovery in a model of TMA-induced renal injury.	VEGF therapy increased glomerular and peritubular MV density and decreased ischemia.
VEGF-165 ^{18, 20}	Experimental	Intra-renal administration of VEGF to reverse renal dysfunction and injury in experimental RVD.	VEGF therapy improved RBF, GFR, renal perfusion, and increased renal MV density.
VEGF-165 ³⁵	Experimental	Intra-muscular VEGF therapy to stimulate heart regeneration in cardiac failure.	Low-dose VEGF improved tissue regeneration and cardiac muscle activation.
VEGF-165 ^{38, 39}	Clinical	Intra-coronary VEGF to stimulate cardiac function in coronary artery disease.	Low-dose VEGF improved cardiac muscle perfusion.
VEGF-165 ⁹¹	Clinical	Direct myocardial gene transfer of VEGF.	VEGF therapy reduced angina and unchanged/improved ejection fraction.
HGF ⁶⁰	Experimental	Intra-renal administration of rh- HGF to protect the kidney in chronic RVD	HGF therapy improved renal function, renal MV remodeling and fibrosis.
HGF ⁹²	Experimental	To augment angiogenesis in skeletal muscle ischemia using combined VEGF/HGF	Combined VEGF/HGF increased blood flow and capillary density.
HGF ⁹³	Experimental	HGF therapy to decrease brain injury and improve neurologic recovery after stroke.	HGF promotes neuroprotection, proliferation, and cell survival.
HGF ⁹⁴	Experimental	To study the role of HGF therapy in podocyte homeostasis, injury, and repair in vivo.	HGF treatment reduced podocyte damage and death (apoptosis)
HGF ⁵⁴	Experimental	To study the effects of HGF on progression of renal injury in chronic renal disease.	HGF induced fibrinolytic pathways by increasing expression of MMP-9 and decreasing TIMP-2 and PAI-1.
HGF ⁶³	Clinical	To evaluate intramuscular gene transfer using naked plasmid DNA-coding HGF in critical limb ischemia.	HGF significantly increased ankle-brachial index and decreased ulcer size.
b-FGF ⁹⁵	Experimental	To determine the effects of administration of b-FGF in gastrocnemius muscles.	Intramuscular b-FGF increased vascular density in gastrocnemius muscles.
b-FGF ⁹⁶	Experimental	To study the possible protective effects of b- FGF on CsA induced nephrotoxicity.	b-FGF increased kidney vessels and protects against nephrotoxicity.
b-FGF ⁹⁷	Experimental	To determine effects of b-FGF therapy on myocardial function and blood flow in myocardial ischemia.	Administration of b-FGF improved coronary flow and reduced infarct size.
HIF-1 α ⁷³	Experimental	To determine feasibility of HIF-1 α therapy in diabetic critical limb ischemia.	Intramuscular HIF-1 α increased vessel density, perfusion and function, and reduced tissue necrosis
HIF-1 α ⁹⁸	Experimental	To determine feasibility of HIF-1 α in wound healing.	HIF-1 α therapy accelerate wound healing
HIF-1 α ⁹⁹	Experimental	To determine effect of intramuscular delivery of active HIF-1 α .	HIF-1 α delivery improved tissue perfusion and vascular remodeling.
HIF-1 α ⁷⁴	Experimental	To determine role of HIF-1 α in regulating oxygen homeostasis and VEGF.	Administration of HIF-1 α improved angiographic score and blood flow.
PDGF-C ⁸⁷	Experimental	To determine the effects of PDGF infusion or inhibition in glomerulonephritis.	PDGF infusion reduced mesangiolysis and increased glomerular endothelial cell area and proliferation.
PDGF-C ¹⁰⁰	Experimental	To determine the effects of inhibiting PDGF in unilateral ureteral obstruction.	Inhibition of PDGF reduces renal inflammation and fibrosis.