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Angiogenesis in the kidney: a new therapeutic target?

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Abstract

Purpose of review—The prevalence of chronic kidney disease has been growing consistently for the past decades. Renal failure is often associated with defective angiogenesis, and recognition of the contribution of the renal microcirculation to the progression of chronic renal disease may aid in the development of therapeutic interventions.

Recent findings—Intra-renal proliferation, remodeling, and/or rarefaction of microvessels in response to injury can all aggravate nephron damage, and experimental evidence suggests that they may constitute the early steps in the complex pathways involved in progressive renal injury. Recent studies showed the benefits of targeted interventions deemed to promote neovascularization (e.g. progenitor cells, growth factors) on the ischemic myocardium and brain and in a few models of renal disease.

Summary—Evidence of aberrant renal microvascular architecture in various forms of renal disease provides the impetus to attempt modulating the renal microcirculation to interfere with the disease process. Targeted interventions to preserve the renal microcirculation may not only decrease the evolving injury in renal vascular disease but also potentially constitute a coadjuvant intervention to become part of a comprehensive management plan to improve the success of parallel strategies to preserve renal function, such as revascularization.

Keywords

angiogenesis; kidney; microcirculation; vascular rarefaction

Introduction

The prevalence of renal disease has been growing consistently for the past 30 years. Chronic kidney disease affects 16.8% of the US adult population aged 20 years or older, showing an increase in prevalence of over 16% during the last decade [1,2]. Furthermore, end-stage renal disease has been growing at a rate of 8–14% per year for the past 20 years and is expected to double during the next 15 years [3]. Incident end-stage renal disease has outpaced growth in prevalent chronic renal insufficiency [4] and consumes around 6.4% of the total Medicare budget [5]. This alarming increase in chronic and end-stage renal disease is accompanied and promoted by a growing prevalence of cardiovascular risk factors such as obesity, diabetes, and

hypertension that increase the overall morbidity and mortality in these patients. Unfortunately, these reports underscore that these numbers are still far from decreasing. Therefore, there is an urgent need to identify the mechanisms that perpetuate and aggravate renal dysfunction and scarring, and to develop strategies to prevent and attenuate them.

Most chronic renal diseases are complicated by renal inflammation and fibrosis, leading to a progressive deterioration of renal function, and potentially ultimately resulting in irreversible renal failure. Others and we have previously shown the presence of inflammation [6,⁷], tubulointerstitial fibrosis, and glomerulosclerosis [8,⁹] in the kidney exposed to a chronic insult such as atherosclerosis, diabetes [10], hypertension [11], and renal ischemia [8,⁹]. Advanced tubulointerstitial damage is often associated with the loss of peritubular capillaries [12]. Progressive renal disease is indeed characterized by progressive deterioration of the renal microvasculature, which correlates with the development of glomerular and tubulointerstitial fibrosis [13]; however, we have previously shown that alterations in the renal microvascular architecture may differ depending on the renal insult triggering microvascular proliferation [14,¹⁵] or rarefaction [16,¹⁷]. More intriguing is the fact that, despite these opposing effects on the renal microvascular architecture, renal injury in these models remains significant, raising a question about the physiological benefit of renal microvascular proliferation.

Microvascular proliferation in the kidney: the more, the better?

The ability of microvascular networks to adapt to the metabolic local conditions by upregulating or downregulating vascular proliferation is a feature known as microvascular plasticity [18]. Neovascularization is a major physiological response to ischemia that involves a sequence of events resulting in development of new capillaries from endothelial cells or preexisting vessels. Although we intuitively tend to link angiogenesis to a compensatory response of the ischemic tissue to a lack of blood flow and oxygen supply, generation of new vessels also plays a role in other processes such as wound healing [19], and excess neovascularization could even be pathological in situations such as chronic inflammatory diseases [20], malignancies [21], and diabetic retinopathy [22] and nephropathy [23*].

We have previously shown evident renal neovascularization in experimental hypercholesterolemia [14,¹⁵], a surrogate and cause of atherosclerosis. It is possible that the trigger for neovascularization in this milieu is subtle ischemia due to functional microvascular 'rarefaction' as a result of renal vasoconstriction, mediated by endothelial dysfunction and increased oxidative stress. Alternatively, considering that ample blood and oxygen supplies the kidney under basal conditions, renal neovascularization in the early stage of atherosclerosis might be promoted by inflammation, an important mediator of angiogenesis. Irrespective of the cause, these new vessels likely represent a 'response to injury' of the hypercholesterolemic kidney deemed to sustain renal perfusion. Indeed, inhibition of vascular proliferation using thalidomide, an anti-inflammatory and antiangiogenic drug, substantially decreased basal renal hemodynamics and function in this model [24]; however, thalidomide also restored renovascular endothelial function, suggesting that the new microvessels in the hypercholesterolemic kidney were dysfunctional. Newly generated vessels may present a disorganized architecture, functional abnormalities, increased permeability, or blind endings [25,²⁶]; therefore leading to deficient regulation and delivery of blood flow. Indeed, maturation of the endothelial network involves remodeling and 'pruning' of irregularly organized vessels into a structured network of branching vessels [27], and specific molecular cues for vascular maturation (such as platelet-derived growth factor-BB) may be necessary in order to ensure robust and stable microvascular beds. It is not unlikely that new fragile and disorganized microvessels in fact exacerbate tissue injury, and that pruning of such vessels may be favorable. Hence, an increase in the number of vessels alone may not necessarily benefit the kidney (Fig.

1), especially since inflammation, tubulointerstitial fibrosis, and vascular remodeling are evident despite increased neovascularization [14,15].

On the contrary, insufficient angiogenesis or loss of peritubular and glomerular capillaries have been observed in renal disease models such as the remnant kidney model of progressive renal failure [28], aging [13], ischemia [14,17], glomerulonephritis [29], and acute ischemic renal failure [30], suggesting a role for small vessels in modulating renal injury. It is not clear whether microvascular loss is a primary cause or is secondary to renal injury, or even a parallel process that further contributes to renal damage as renal disease progresses; however, it is likely the result of combined functional (e.g. vasoconstriction) and structural (e.g. remodeling or regression) vascular rarefaction. Microvascular loss is consequential, as our studies in experimental renal artery stenosis, a major cause of renovascular hypertension and ischemic nephropathy, showed that a reduction in the diameter and density of cortical microvessels in the obstructed kidney was accompanied by decreased renal blood flow and glomerular filtration rate, tubulointerstitial and perivascular fibrosis, and glomerulosclerosis [8]. In fact, it is possible that microvascular loss is preceded by early capillary and microvascular proliferation to offset a fall in the number of nephrons, but the proliferation cannot be sustained over time owing to apoptosis [31]. Moreover, because angiogenic microvessels are often abnormal in structure and function, they may be more frail and prone to regression. Accumulation of extracellular matrix (ECM) may also physically interfere with endothelial cell migration into the perivascular space, capillary sprouting, and microvascular development, and ECM molecules such as thrombospondin-1 can exert antiangiogenic effects by inhibiting endothelial cell proliferation, migration, and tube formation [32]. Microvascular inward remodeling [16, 17] may further reduce renal microvascular diameter and decrease blood flow, which in turn facilitates the build up of intra-renal fibrosis that may further constrain and limit new microvascular growth and development [33], ultimately promoting microvascular rarefaction and consequently renal injury (Fig. 1) through a positive feedback mechanism.

Hence, the renal microvasculature likely modifies its architecture depending on the needs of the kidney, underscoring microvascular plasticity as an active process in renal disease that may modify the responses of the kidney depending on the insult.

Renal microcirculation: a target for therapeutic interventions in renovascular disease?

The evidence for aberrant microvascular architecture in various forms of renal disease provides the impetus to modulate the renal microcirculation in an attempt to interfere with the disease process. For example, renovascular disease is characterized by intra-renal microvascular disease that possibly aggravates the effects of the obstruction in the main renal artery and exacerbates the progression of renal injury. It is likely that intra-renal microvascular disease precedes the onset and represents the silent phase of ischemic renal disease [34], and, as the damage of the renal parenchyma progresses, the deterioration of the kidney advances and becomes irreversible. The severity and persistence of damage to the intra-renal microvascular bed may be one reason for the failure of renal function to improve in the majority of patients with atherosclerotic renovascular disease after complete renal revascularization [35], highlighting a pressing clinical need. Furthermore, this lack of success in salvaging the kidney supports the notion that ongoing injurious mechanisms distal to the stenosis determine the fate of the kidney beyond the obstruction.

Understanding the molecular mechanisms that lead to microvascular proliferation or regression may provide opportunities for prevention or therapeutic interventions (Fig. 2). Our previous studies in a swine model of renovascular disease have shown that a chronic reduction in blood flow to the kidney results in downregulation of proangiogenic factors such as vascular

endothelial growth factor (VEGF), the most important pathway in angiogenesis [36], as well as its upstream and downstream mediators such as hypoxia-induced factor (HIF)-1 α , Akt, and nitric oxide [14,17]. Unlike acute ischemia, a chronic reduction in blood flow decreases renal expression of angiogenic factors, suggesting a downregulation of the angiogenic cascade, possibly attributable to destabilization of HIF-1 α mRNA by von Hippel–Lindau (VHL) protein or degradation of HIF-1 α protein by reactive oxygen species [37]. As a result, inadequate angiogenesis during chronic renal ischemia may lead to microvascular rarefaction and consequently deficient blood and oxygen supply to the ischemic kidney. An imbalance in renal angiogenic factors in renal disease has been shown to be accompanied by renal upregulation of antiangiogenic factors, such as thrombospondin-1 [13], possibly mediated by cytokines or oxidative stress. Hence, targeting these pathways by therapeutic interventions to preserve microvascular architecture by protecting microvascular function or promoting their proliferation may have an impact on renal function.

Recent studies have shown the capability of endothelial or mesenchymal progenitor cells as a targeted intervention to promote vasculogenesis in the ischemic myocardium [38**] and brain [39]. Furthermore, a few recent reports demonstrated potential for the use of progenitor cells for the injured kidney in glomerulonephritis [40,41] and acute ischemia reperfusion [42]. It is not unlikely that a large part of their beneficial effects in the kidney is mediated by an increase in both microvascular proliferation and maturation [43**], because the paracrine impact of progenitor cells on the kidney involves concurrent secretion of a variety of angiogenic factors. It is of interest that the kidney not only could be a target for intervention using progenitor cells, but is also a source for these cells [43**,44], and has been shown in patients to increase their production in renovascular disease [45]. Further studies are needed to establish the efficacy of this approach to restore the renal microvasculature in chronic kidney diseases. Other potential approaches to augment vasculogenesis could employ delivery of growth factors such as VEGF, which has been shown to improve the perfusion of the ischemic myocardium [46], and to promote repair and reverse renal capillary loss in experimental glomerulonephritis [47]. Furthermore, our previous studies have shown that clinically available agents such as antioxidants [14,48], endothelin-receptor blockers [15], and statins [17] can preserve renal microcirculatory function, promote microvascular proliferation and stabilization, and decrease microvascular damage, in conjunction with improvement in renal function. Conceivably, strategies that blunt apoptosis may also potentially limit microvascular loss during the transition phase from acute to chronic renal disease.

Conclusion

Restoration of blood flow to the site of injured tissue is crucial for developing a successful repair response. Generation of new vessels in the kidney is not confined to the developmental phase but seems to be a mechanism that is activated in response to injury, likely to preserve renal function; however, an orchestrated sequence of events is crucial for that response to be beneficial for the kidney and dysregulated formation of new vessels can be deleterious. It is possible that the damage to the renal microvascular architecture and deterioration of the angiogenic response constitute the early steps in the complex multiple pathways involved in progressive renal injury (Fig. 2). Identifying means to predict the ‘point of no return’ for renal parenchymal injury and when renal function may still be salvageable is in dire need. Considering that the generation of new vessels as a compensatory mechanism may be exhausted or negated during sustained and progressive renal injury, targeted interventions to preserve the renal microcirculation may not only decrease the evolving injury in renal vascular disease but also potentially constitute a coadjuvant intervention to improve the success of parallel strategies to improve renal function, such as revascularization. Carefully designed prospective experimental and clinical studies are needed to advance our knowledge for

appropriate utilization of therapeutic options and the timing of deployment of interventional techniques to improve the outcomes of patients with chronic renal disease.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Prevalence of chronic kidney disease and associated risk factors: United States, 1999–2004. *MMWR Morb Mortal Wkly Rep* 2007;56:161–165. [PubMed: 17332726]
2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038–2047. [PubMed: 17986697]
3. USRDS 2007 annual data report: atlas of end-stage renal disease in the United States, National Institutes of Health. USRDS; Minneapolis: 2007. <http://www.usrds.org/adr.htm>
4. Hsu CY, Vittinghoff E, Lin F, et al. The incidence of end-stage renal disease is increasing faster than the prevalence of chronic renal insufficiency. *Ann Intern Med* 2004;141:95–101. [PubMed: 15262664]
5. Hallan SI, Vikse BE. Relationship between chronic kidney disease prevalence and end-stage renal disease risk. *Curr Opin Nephrol Hypertens* 2008;17:286–291. [PubMed: 18408480]
6. Vidt DG. Inflammation in renal disease. *Am J Cardiol* 2006;97(2A):20A–27A.
7. Stenvinkel P. Inflammation in end-stage renal disease: a fire that burns within. *Contrib Nephrol* 2005;149:185–199. [PubMed: 15876843]
8. Chade AR, Rodriguez-Porcel M, Grande JP, et al. Distinct renal injury in early atherosclerosis and renovascular disease. *Circulation* 2002;106:1165–1171. [PubMed: 12196346]
9. Chade AR, Rodriguez-Porcel M, Grande JP, et al. Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. *Arterioscler Thromb Vasc Biol* 2003;23:1295–1301. [PubMed: 12750121]
10. Coimbra TM, Janssen U, Grone HJ, et al. Early events leading to renal injury in obese Zucker (fatty) rats with type II diabetes. *Kidney Int* 2000;57:167–182. [PubMed: 10620198]
11. Rodriguez-Porcel M, Krier JD, Lerman A, et al. Combination of hypercholesterolemia and hypertension augments renal function abnormalities. *Hypertension* 2001;37:774–780. [PubMed: 11230372]
12. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. *J Am Soc Nephrol* 2006;17:17–25. [PubMed: 16291837]
13. Kang DH, Anderson S, Kim YG, et al. Impaired angiogenesis in the aging kidney: vascular endothelial growth factor and thrombospondin-1 in renal disease. *Am J Kidney Dis* 2001;37:601–611. [PubMed: 11228186]
14. Chade AR, Bentley MD, Zhu X, et al. Antioxidant intervention prevents renal neovascularization in hypercholesterolemic pigs. *J Am Soc Nephrol* 2004;15:1816–1825. [PubMed: 15213269]
15. Chade AR, Krier JD, Textor SC, et al. Endothelin-a receptor blockade improves renal microvascular architecture and function in experimental hypercholesterolemia. *J Am Soc Nephrol* 2006;17:3394–3403. [PubMed: 17082239]
16. Zhu XY, Chade AR, Rodriguez-Porcel M, et al. Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress. *Arterioscler Thromb Vasc Biol* 2004;24:1854–1859. [PubMed: 15308558]

17. Chade AR, Zhu X, Mushin OP, et al. Simvastatin promotes angiogenesis and prevents microvascular remodeling in chronic renal ischemia. *FASEB J* 2006;20:1706–1708. [PubMed: 16790524]
18. Ebrahimian TG, Heymes C, You D, et al. NADPH oxidase-derived overproduction of reactive oxygen species impairs postischemic neovascularization in mice with type 1 diabetes. *Am J Pathol* 2006;169:719–728. [PubMed: 16877369]
19. Eming SA, Brachvogel B, Odorisio T, et al. Regulation of angiogenesis: wound healing as a model. *Prog Histochem Cytochem* 2007;42:115–170. [PubMed: 17980716]
20. Chaparro M, Sanz-Cameno P, Trapero-Marugan M, et al. Mechanisms of angiogenesis in chronic inflammatory liver disease. *Ann Hepatol* 2007;6:208–213. [PubMed: 18007549]
21. Folkman J. The role of angiogenesis in tumor growth. *Semin Cancer Biol* 1992;3:65–71. [PubMed: 1378311]
22. Hernandez C, Simo R. Strategies for blocking angiogenesis in diabetic retinopathy: from basic science to clinical practice. *Expert Opin Invest Drugs* 2007;16:1209–1226.
23. Zent R, Pozzi A. Angiogenesis in diabetic nephropathy. *Semin Nephrol* 2007;27:161–171. Comprehensive review describing the major factors involved in the pathologic glomerular microvascular alterations in diabetic nephropathy and the possible use of antiangiogenic therapies for the treatment of this disease. [PubMed: 17418685]
24. Chade AR, Krier JD, Galili O, et al. Role of renal cortical neovascularization in experimental hypercholesterolemia. *Hypertension* 2007;50:729–736. [PubMed: 17635852]
25. Dvorak HF, Brown LF, Detmar M, et al. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *Am J Pathol* 1995;146:1029–1039. [PubMed: 7538264]
26. Gerwins P, Skoldenberg E, Claesson-Welsh L. Function of fibroblast growth factors and vascular endothelial growth factors and their receptors in angiogenesis. *Crit Rev Oncol Hematol* 2000;34:185–194. [PubMed: 10838264]
27. Carmeliet P. Angiogenesis in health and disease. *Nat Med* 2003;9:653–660. [PubMed: 12778163]
28. Kang DH, Hughes J, Mazzali M, et al. Impaired angiogenesis in the remnant kidney model: II. Vascular endothelial growth factor administration reduces renal fibrosis and stabilizes renal function. *J Am Soc Nephrol* 2001;12:1448–1457. [PubMed: 11423573]
29. Hara A, Wada T, Furuichi K, et al. Blockade of VEGF accelerates proteinuria, via decrease in nephrin expression in rat crescentic glomerulonephritis. *Kidney Int* 2006;69:1986–1995. [PubMed: 16641924]
30. Basile DP. Rarefaction of peritubular capillaries following ischemic acute renal failure: a potential factor predisposing to progressive nephropathy. *Curr Opin Nephrol Hypertens* 2004;13:1–7. [PubMed: 15090853]
31. Kang DH, Kanellis J, Hugo C, et al. Role of the microvascular endothelium in progressive renal disease. *J Am Soc Nephrol* 2002;13:806–816. [PubMed: 11856789]
32. Sottile J. Regulation of angiogenesis by extracellular matrix. *Biochim Biophys Acta* 2004;1654:13–22. [PubMed: 14984764]
33. Schrijvers BF, Flyvbjerg A, De Zeeuw AS. The role of vascular endothelial growth factor (VEGF) in renal pathophysiology. *Kidney Int* 2004;65:2003–2017. [PubMed: 15149314]
34. Meyrier A, Hill GS, Simon P. Ischemic renal diseases: new insights into old entities. *Kidney Int* 1998;54:2–13. [PubMed: 9648058]
35. Textor SC. Atherosclerotic renal artery stenosis: overtreated but underrated? *J Am Soc Nephrol* 2008;19:656–659. [PubMed: 18235081]
36. Gross ML, Adamczak M, Amann K, et al. Mediators of inflammatory and ischemic renal damage: the role of neoangiogenesis. *J Nephrol* 2005;18:513–520. [PubMed: 16299676]
37. Zou AP, Cowley AW Jr. Reactive oxygen species and molecular regulation of renal oxygenation. *Acta Physiol Scand* 2003;179:233–241. [PubMed: 14616239]
38. Rota M, Padin-Iruegas ME, Misao Y, et al. Local activation or implantation of cardiac progenitor cells rescues scarred infarcted myocardium improving cardiac function. *Circ Res* 2008;103:107–116. Outstanding report describing the beneficial effects of cardiac progenitor cells (CPCs) in cardiac repair. CPCs synthesize matrix metalloproteinases that degraded collagen proteins, forming

tunnels within the fibrotic tissue during their migration across the scarred myocardium, suggesting CPCs as ideal candidate cells for cardiac repair. [PubMed: 18556576]

39. Takagi Y, Nishimura M, Morizane A, et al. Survival and differentiation of neural progenitor cells derived from embryonic stem cells and transplanted into ischemic brain. *J Neurosurg* 2005;103:304–310. [PubMed: 16175861]
40. Uchimura H, Marumo T, Takase O, et al. Intrarenal injection of bone marrow-derived angiogenic cells reduces endothelial injury and mesangial cell activation in experimental glomerulonephritis. *J Am Soc Nephrol* 2005;16:997–1004. [PubMed: 15744001]
41. Abe-Yoshio Y, Abe K, Miyazaki M, et al. Involvement of bone marrow-derived endothelial progenitor cells in glomerular capillary repair in habu snake venom-induced glomerulonephritis. *Virchows Arch* 2008;453:97–106. [PubMed: 18551312]
42. Togel F, Hu Z, Weiss K, et al. Administered mesenchymal stem cells protect against ischemic acute renal failure through differentiation-independent mechanisms. *Am J Physiol Renal Physiol* 2005;289:F31–F42. [PubMed: 15713913]
- 43••. Chen J, Park HC, Addabbo F, et al. Kidney-derived mesenchymal stem cells contribute to vasculogenesis, angiogenesis and endothelial repair. *Kidney Int* 2008;74:879–889. Outstanding paper showing the capabilities of kidney mesenchymal stem cells to differentiate towards endothelial and smooth muscle cell phenotypes *in vivo* and *in vitro*. [PubMed: 18596729]
44. Gupta S, Verfaillie C, Chmielewski D, et al. Isolation and characterization of kidney-derived stem cells. *J Am Soc Nephrol* 2006;17:3028–3040. [PubMed: 16988061]
45. Fadini GP, Miotto D, Baesso I, et al. Arterio-venous gradient of endothelial progenitor cells across renal artery stenosis. *Atherosclerosis* 2005;182:189–191. [PubMed: 15939422]
46. Hendel RC, Henry TD, Rocha-Singh K, et al. Effect of intracoronary recombinant human vascular endothelial growth factor on myocardial perfusion: evidence for a dose-dependent effect. *Circulation* 2000;101:118–121. [PubMed: 10637195]
47. Masuda Y, Shimizu A, Mori T, et al. Vascular endothelial growth factor enhances glomerular capillary repair and accelerates resolution of experimentally induced glomerulonephritis. *Am J Pathol* 2001;159:599–608. [PubMed: 11485918]
48. Chade AR, Rodriguez-Porcel M, Herrmann J, et al. Antioxidant intervention blunts renal injury in experimental renovascular disease. *J Am Soc Nephrol* 2004;15:958–966. [PubMed: 15034098]

Figure 1. Representative three-dimensional reconstruction of the renal microvascular architecture (using microcomputed tomography) and renal morphology (trichrome staining) showing opposing changes in microvascular architecture in early atherosclerosis compared with chronic ischemia (top) Scale bar (trichrome): 25 μm

Microvascular rarefaction in particular is accompanied by severe renal fibrosis (bottom). MV, microvascular.

Figure 2. Schematic illustration of the potential mechanisms that modulate renal vascular proliferation and loss

At the early stage of renal injury, compensatory mechanisms induce microvascular proliferation, but abnormal microvascular structure and function, continuous oxidative stress, and accumulation of extracellular matrix (ECM) subsequently result in microvascular loss. These mechanisms suggest a complex sequence of stimuli on the renal microcirculation that may ultimately lead to progressive and, likely, irreversible renal injury. MV, microvascular.