Activated Pericytes and the Inhibition of Renal Vascular Stability: Obstacles for Kidney Repair

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The hallmark feature of CKD and its progression to end stage is the presence and severity of interstitial fibrosis.1,2 This long-recognized association is the prime driving force of research to understand the nature of renal scarification. Much of the research in this area can be grouped into one of two broad categories: efforts geared toward understanding the biochemical and pathophysiological factors that govern the degree of progression and efforts aimed at defining the cellular and molecular elements that comprise renal scars. With regard to the former, it is clear that a profibrotic environment is promoted by activity from a variety of factors with activity driving the production of extracellular matrix (ECM). Of these, TGFβ and other profibrotic cytokines have been widely studied, and these are enhanced by local tissue injury, epithelial cell cycle arrest, cell differentiation status, or hypoxia.1,3

With regard to the latter, although multiple cell types produce ECM, myofibroblasts are considered a primary contributor to ECM production in interstitial fibrosis.3 Nevertheless, there has been considerable debate regarding the origin of these interstitial cells and whether they derive from proliferation, circulating fibrocytes, or transition from either epithelial or endothelial sources (EMT or EndoMT). Recently, compelling evidence indicates that myofibroblasts may derive from activated pericytes following detachment from the endothelial cells (ECs) for which they provide support.4 Although specific arguments for each of the potential sources are beyond the scope of this editorial, a comprehensive perspective on progressive fibrosis requires accommodation of theories regarding both the origin and acceleration of renal scarring.

Interestingly, a central common feature present in virtually all models leading to interstitial fibrosis is the reduction in peritubular capillary (PTC) density, which is thought to fuel hypoxia and accelerate the rate of fibrosis by directly influencing pathways of ECM production.1 To date, there is very little known about the mechanism mediating PTC endothelial cell loss or the apparent inability to undergo successful repair. That both increased interstitial fibroblast deposition and reduced PTC density occur in the same setting raises the possibility that the two processes are mechanistically linked. One possibility, for which there is some evidence, is that injury promotes endothelial-mesenchymal transition, which simultaneously increases fibroblast number while decreasing vascular cell populations.5,6 A second possibility exists in which pericyte differentiation into myofibroblasts reduces endothelial trophic activity resulting in capillary rarefaction. In our opinion, these possibilities are not mutually exclusive.

In the current issue of JASN, Schrimpf et al.7 address the hypothesis that PTC reduction after injury is the result of failed maintenance by pericytes following their activation and differentiation into myofibroblasts. The investigators isolated naïve pericytes or activated pericytes following unilateral ureteral obstruction and, by microarray analysis, demonstrated that pericyte activation was characterized by increased production of the antiangiogenic factor ADAMTS-1, a disintegrin and metalloproteinase with thrombospondin motifs-1, and the downregulation of its inhibitor, tissue inhibitor of metalloproteinase-3 (TIMP-3). Human ECs form capillary networks in 3D collagen gels, which regress following exposure to the serine protease kallikrein. The authors cleverly used this phenomenon to demonstrate that coculture with pericytes stabilized EC capillary networks in response to the destructive stimulus, whereas activated pericytes fail to stabilize ECs. Interestingly, exogenous ADAMTS-1 completely blocked the ability of pericytes to stabilize capillaries, whereas TIMP-3 supplementation attenuated the destruction of capillary networks by kallikrein in the absence of pericytes. The authors also noted that Timp 3−/− mice are predisposed to interstitial fibrosis and that pericytes from these animals appear to be activated and express high levels of ADAMTS-1. Moreover, these mice demonstrate a more severe capillary loss and fibrosis in response to a mild ischemia/reperfusion (I/R) injury than wild types.7

These elegant studies provide insight at the molecular and cellular level into the link between fibrosis and capillary loss after injury and, importantly, are compatible with existing dogma regarding progressive CKD. Clearly, peritubular capillary loss represents a primary component driving fibrosis according to the chronic hypoxia hypothesis,1 but the basis for sustained vascular loss in the face of hypoxia is unclear. Why does the endothelium not repair itself? Several viewpoints exist including the loss of trophic factors, particularly vascular endothelial growth factor (VEGF) that maintain the endothelium of the renal microvasculature. VEGF is produced by epithelial cells, and its expression is lost in models of interstitial fibrosis.8 Germane to this view is the observation that blockade of VEGF results in regression of the renal microvasculature.9

Similarly, there are reports in models of fibrosis that demonstrate the generation of antiangiogenic factors including proteolytic fragments of the basement membrane.10,11 Metalloproteinases, such as ADAMTS-1 and the gelatinases, are
important in the generation of some of these angio-inhibitory factors and the activity of VEGF splice variants. These metalloproteinases may be produced by affected epithelial cells, endothelial cells, or as demonstrated by the authors for ADAMTS-1, activated pericytes.

A third possibility posed by us is that renal endothelial cells fail to undergo a significant proliferative response. It is noteworthy that there are very few studies successfully demonstrating sustained cultures of rodent kidney-derived endothelial cells without the aid of viral or transgenically mediated transformation. Although this may be considered a technical limitation, it likely reflects a failure of these cells to thrive in culture conditions because of a lack of intrinsic growth potential. This is in stark contrast to renal epithelial cells, which proliferate robustly in rodent injury models to repair damaged kidneys. However, the tubular epithelial proliferative capacity is not limitless. The proliferative potential of tubular cells derived from aging kidneys is reduced relative to young animals, coinciding with their reduced reparative ability. By extension, we suggest that the loss of PTC should be viewed not only in terms of the surrounding trophic environment, but also whether these cells, once stimulated, can be induced to proliferate. On this final point, we highlight that, although many strategies have been used to preserve the loss of PTCs in response to an injury (VEGF-121, angiopoietin-1), we are not aware of any study demonstrating that these strategies can revascularize a kidney once rarefaction is established.

Like many intriguing studies, this provides a new perspective while also stimulating new questions. The current study provides strong evidence that activated pericytes lose their ability to provide adequate protection to endothelial cells. However, pericyte activation occurs following detachment from the endothelium, highlighting that a state of dynamic reciprocity exists between these two cell types. This scenario gives rise to a chicken-and-egg argument in which injury may be directed toward either cell type initially, with either leading to a similar outcome. Thus, we could envision that alterations in endothelial structure in response to injury contribute to the pericyte activation process, which subsequently reduces endothelial survival and regeneration.

In support of this, we highlight the connection between the activation of matrix metalloproteinases and both acute and chronic alterations in endothelial function. Matrix metalloproteinases (MMPs) are well known to play a role in angiogenesis, but their pathologic expression may result in vascular impairing following acute ischemic injury. The gelatinases, MMP2 and MMP9, are activated in kidney after I/R. The loss of endothelial barrier function of the PTCs is an early manifestation of the increased permeability of the renal capillaries can be attenuated by pharmacological blockade of the gelatinases. Whether these early alterations in PTC endothelial structure relate to long-term function and chronic instability of capillaries remains unclear. However, recent work suggests that PTC rarefaction is significantly attenuated in MMP-9–null mice following I/R injury, suggesting that similar molecular pathways that mediate both the early endothelial response and chronic changes in vascular stability.

Placed in context, it is tempting to speculate that rapidly activated alterations in endothelial structure and function, apparently linked to gelatinase activity, may initiate detachment from pericytes and set in motion the coordinated processes culminating in vascular dropout. Indeed, the authors have shown that placed reduced TIMP-3 activity in the crosshairs of the pericyte activation process. While TIMP-3 inhibits ADAMTS-1, it also is a known inhibitor of both MMP-2 and MMP-9 activity. The further investigation into these processes is likely to generate additional complexity into the process of pericyte activation and the regulation of capillary stability following injury.

Regardless of lingering questions relating to the proliferative capacity of renal endothelial cells or the further characterization of the metalloproteinase environment either mediating pericyte activation or resulting from pericyte activation, the implications raised by this paper are profoundly important. When one becomes interested in understanding limitations on the potential to revascularize damaged kidneys, consideration of efforts to stimulate endothelial growth (or endothelial replacement) may be futile if pericytes remain activated. Hopefully, the identification of this biologic barrier will help to provide a rational strategy to promote vascular repair and slow the development of renal fibrosis.

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DISCLOSURES

None.

REFERENCES


The Impact of Renal Function on Outcomes of Bariatric Surgery

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In this issue of JASN, Turgeon et al.1 offer new insights into the relationship between complications from bariatric surgery and kidney function measured by GFR. They report a positive correlation between stage of kidney disease and complication rate. Given significantly higher complication rates in weight loss surgery patients, they recommend careful consideration of potential adverse effects. At the same time, they acknowledge that benefits may outweigh the higher risks of bariatric surgery in these cases.

The public health crisis of obesity in America has fueled growth in the number of candidates for bariatric procedures.2 At the same time, improved safety measures and greater surgical precision have led to a decline in complication rates. This has enabled weight loss surgery to be performed in previously unqualified patients. Among these are diabetic individuals3 with a body mass index <35 kg/m².

As the number of procedures in patients with CKD increases, treatment guidelines will develop. These will reduce the risk of complications while allowing access to the advantages of surgery, including successful weight loss and improved parameters of kidney function.

Nonetheless, a number of problems still hinder understanding of the risk-to-benefit ratio of bariatric surgery in CKD patients. Turgeon et al. used estimated GFR to classify patients by CKD stage. However, there has been increasing debate over the use of GFR as a marker of kidney function in the obese population.4 Controversy centers on which equation best estimates GFR and whether it should be adjusted to account for the higher average body surface area (BSA) in these patients (1.9 m²).

Indexing GFR according to the standard BSA of 1.73 m² underestimates the rate in patients with larger BSAs. Nair et al.5 also found that the Modification of Diet in Renal Disease (MDRD) equation, which uses an index of 1.9 m², also under-estimated GFR in diabetic patients with obesity. Although no estimated GFR equation has been validated,6 Michels et al.7 reported that the CKD-Epi formula outperformed both the Cockroft-Gault and MDRD in accurately estimating GFR in obese populations.

GFR tends to be underestimated in obese patients, including those with diabetes. Indeed, debate is ongoing over whether creatinine-based or cystatin C–based GFR estimation is more accurate in these patients.8 A way to accurately estimate GFR in weight loss surgery patients is needed to assess kidney function before and after procedures. However, that goal is elusive, complicated by both body size and the body composition changes that occur as a result of surgery.9

Although there is no perfect way to determine kidney function using GFR, Turgeon et al. show that kidney status has a profound impact on surgical outcomes. Effective measurement can help identify and prevent complications. It can also serve as a means by which clinicians can determine the type of surgery that will provide the best balance between risks and potential gains.

Malabsorptive surgeries can lead to kidney failure even in patients without prior renal dysfunction because of increased hyperoxaluria.10,11 In one report on Roux-en-Y gastric bypass (RYGB), 7.65% of RYGB patients developed hyperoxaluria compared with only 4.63% of controls.10 However, gastric banding or sleeve gastrectomy do not increase urinary oxalate excretion.12,13 Purely restrictive procedures are less likely to result in the development or exacerbation of CKD.14

Although restrictive procedures have lower complication and mortality rates, RYGB has the best weight loss outcomes.15 For