Renal vascular pericytes – long overlooked and poorly understood, but clearly important

– and what about those regulatory pathways?

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Running Head: Vascular pericytes and red blood cell congestion

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Ischemic kidney injury involves multiple dynamic processes, not limited to but including inflammation, endothelial and epithelial cell disruption and changes in hemodynamics. Failure to understand the complexities of renal vascular structure and function has been a persistent barrier to fully understanding the etiology of kidney injury. Long considered to be involved with regulation of blood flow in medullary vasa recta, pericytes have increasingly been recognized as playing multifactorial roles in vascular integrity and overall renal function in health and disease (6). In a recent study published in this journal, Crislip and his colleagues (3) have demonstrated in rats, that a full complement of pericytes along the vasa recta may be key to limiting outer medullary vascular red blood cell congestion, thereby reducing post-ischemic kidney injury.

Pericytes are contractile cells embedded within the basement membrane of capillaries and which possess elongated processes that encircle the endothelial wall (1). Renal pericytes are associated with glomeruli and cortical and medullary peritubular capillaries as well as with vasa recta. Pericytes have diverse functions, serving as scaffolding cells associated with development and maintenance of vasculature, contributing to hemodynamic processes by way of cell-to-cell signaling along the vessel length and possibly between vessels, influencing axial flows by way of contractile forces, among a host of other functions (9).

The architecture of medullary vasa recta and peritubular capillaries and dynamics of blood flow through these vessels are complex (Fig. 1). Vascular architecture is better known for rodents than for humans, with many similarities, but also significant
differences (11). Efferent arterioles from juxtamedullary glomeruli give rise to the
descending vasa recta, which descend through vascular bundles of the outer and inner
stripes of the outer medulla and continue through the inner medulla. Vasa recta lie in a
close physical association with (rats and mice) or without (humans) short loop
descending thin limbs in a species-dependent manner (10). In the outer medulla and
continuing through much of the inner medulla, descending vasa recta peel off from the
bundle region at all levels and enter the interbundle region, forming complex networks
of peritubular capillaries that carry blood predominantly in an ascending direction,
returning blood to the cortical vasculature. The distinctive architecture of blood vessel
arrays in bundle and interbundle regions is clearly recognizable in transverse tissue
sections.

The renal microvasculature plays critical roles in the pathophysiology and recovery from
post-ischemic acute kidney injury in human allografts (2). For example, disorganization
of F-actin filaments of vascular smooth muscle cells, disruption of endothelial cells and
damage to peritubular pericytes in cortical tissue of cadaveric renal allografts occur
following ischemia-reperfusion (5). The degree of preservation of endothelia and
pericyte cells is positively correlated with recovery in these patients. These types of
studies suggest that a direct correlation exists between renal pericyte density in human
kidney transplants and improved recovery following renal injury.

Physical inaccessibility to the outer and inner medulla imposes limitations on using
intravital imaging and other techniques common to investigating cortical function, and
so, basic static techniques, and infrequently, more invasive approaches are relied upon to study medullary vascular cells and blood flow dynamics. While providing intriguing insights, these approaches have generally not kept pace with recent advances that have been made in understanding more superficial vascular function (4).

Despite these odds, the dynamic characteristics of outer medullary vasa recta and associated pericytes and peritubular capillary structure and function identified by Crislip et al (3), provide insights into new methodologies for studying post-ischemic renal injury and improving clinical outcomes.

Following up on studies that suggest a correlation exists between pericyte density and improved recovery following renal injury, Crislip et al hypothesized that by reducing medullary pericyte density by one of several methods, they would evoke an increase in renal injury. One of those methods was renal ischemia-reperfusion. In order to relate their hypothesis to renal injury outcomes associated with hypertension, they used a spontaneously hypertensive rat strain for their studies. Their key finding: lower outer medullary pericyte density correlates with increased ischemia-reperfusion-induced injury, as hypothesized; most notable was an increase in red blood cell congestion in peritubular capillaries, although increased congestion was not observed in vasa recta.

Perhaps the larger diameter of vasa recta compared to peritubular capillaries and mechanical agitation by pericytes permits better red blood cell clearance in vasa recta, although the tortuous branching of the capillary networks may also be a contributing factor to congestion in peritubular capillaries. While they observed reduced pericyte
density in both males and females, a concurrent increase in arterial plasma creatinine and blood urea nitrogen occurred in females but not males. In the broader view, these sex differences likely point to mechanisms that underlie male and female differences in outcomes of cardiovascular events.

A second method of reducing peritubular capillary density, this one pharmacological, showed similar results – treatment with the ACE inhibitor enalapril, following ischemia reperfusion, resulted in increased red blood cell congestion in both sexes, both in vasa recta as well as in peritubular capillaries. However, creatinine and blood urea nitrogen levels were unaffected by enalapril, at least during the time points examined, thereby raising further questions regarding the links between congestion and injury and congestion and other physiological processes.

The regulatory mechanisms that influence pericyte contraction, endothelial cell function and blood flow through medullary vasa recta and peritubular capillary networks are far from being well-understood. This limits our understanding of broader functional connections between pericyte density, red blood cell congestion and other processes associated with hypertension and renal injury.

A number of locally released vasoactive agents can regulate medullary microcirculation, cell maintenance and structure and function (7). Countercurrent systems that involve axial and lateral solute flows between descending and ascending nephrons and blood vessels recycle signaling molecules and other solutes, retaining them within the
medullary “universe” and generating variably high or low concentrations and likely also axial and lateral gradients (8). Despite their wide influence on a variety of medullary tubulovascular processes, these countercurrent systems and recycling pathways have rarely been quantified, if at all, leaving a huge gap in our ability to model and comprehend these complex flows of signaling molecules and other solutes in vivo.
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Figure 1. Architecture of medullary microcirculation. Descending vasa recta (DVR), ascending vasa recta (AVR). Modified from Pallone et al (8).
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