New insights into mechanisms of glomerular injury and repair from the 10th International Podocyte Conference 2014

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Glomerular kidney diseases are a major cause of end-stage renal disease (ESRD). Thus, it comes as wonderful news that glomerular research is advancing at a remarkable pace. Researchers from around the world met at the 10th International Podocyte Conference in Freiburg, Germany, to discuss the latest developments and findings in this innovative field of kidney research. The meeting highlighted the tremendous progress in our understanding of podocyte-related disorders and promised a rapid transfer of this knowledge into novel treatment options for proteinuric kidney diseases.

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The first 'International Podocyte Conference' was held in Freiburg in 1999 and focused on the understanding of different isolated aspects of podocyte biology. Since then the field has continuously moved forward unraveling the complex integration of podocyte and glomerular biology into the pathophysiological understanding of primary and secondary glomerular diseases. This review shall briefly summarize the current status of podocyte and glomerular biology as it has been presented and discussed during the 2014 International Podocyte Conference (Figure 1).

GLOMERULAR CROSS TALK

During the last couple of years, it has become more and more evident that the cells within the glomerular tuft influence each other via paracrine mechanisms (Figure 2).[1] This function was first established for VEGF-A, which under physiological conditions is regulated in a tightly titrated manner, as both a gradual reduction or an increase in VEGF-A leads to severe glomerular pathologies.[2–5] Although podocyte-derived VEGF-A mainly signals to VEGFR-2 on glomerular endothelial cells, there is also an interesting autocrine loop for podocytes, which relies on VEGFR-1 but not VEGFR-2 signaling.[6] Surprisingly, the soluble variant of VEGFR-1 (sFLT1) seems decisive in mediating this essential loop to maintain podocyte cell morphology and hence glomerular barrier function. It does so by binding to the glycosphingolipid GM3 in lipid rafts on the outside of podocytes, which in turn promotes adhesion and actin reorganization.[6] New evidence points to the specificity of the respective splice isoform of VEGF being involved in this function. VEGF165b has been shown *in vitro* and *in vivo* to be neuroprotective and appears to fulfill a similar role in the kidney.[7] Thus, transgenic mice expressing this isoform are at least partially protected from diabetic albuminuria.

Besides VEGF, new paracrine signaling molecules are entering the stage. One of the most recent examples is endothelin-1, which is produced in podocytes upon stimulation of the TGF-ß cascade, as it occurs in FSGS (focal segmental glomerular sclerosis) or adriamycin-induced

glomerulosclerosis.[8] Endothelin-1 via the endothelin receptor Type A leads to endothelial dysfunction, which in turn augments podocyte stress, finally leading to podocyte depletion.[8] Interestingly, there also seem to be signals that originate in the endothelial cells and relay on to the podocyte. One such example is the thrombomodulin-dependent formation of activated protein C by glomerular endothelial cells. Activated protein C in turn modulates the mitochondrial apoptosis pathway via protease-activated receptor1 (PAR-1) and the endothelial protein C receptor (EPCR), thereby preventing podocyte apoptosis.[9] During glomerular stress as occurs with high glucose in diabetic patients, this pathway is disturbed leading to increased glomerular damage and finally contributing to diabetic nephropathy.[9] Besides the factors mentioned above, there seem to be several others, both of local and systemic origin, which either seem to protect podocytes from injury or modulate injury responses by altering intracellular pathways.[10–12]

Besides the tight interaction between endothelial cells and podocytes across the glomerular basement membrane (GBM), there seems to be potentially equally important cross talk between podocytes and parietal epithelial cells.[13] Presently, research tries to enlighten the signaling pathways involved in this delicate balance between visceral and parietal epithelial cells across Bowman's space. In addition to the initially described HB-EGF pathway in RPGN (rapid progressive glomerulonephritis), more overarching regulators such as miRNAs are recognized and probed as effectors and potential therapeutic targets.[13] Podocytes seem to be versatile players in these intercellular exchanges communicating with all neighboring cells.

In addition, podocytes take center stage for generating and modifying the GBM, for example, in the Alport Syndrome with mutations in the COL 4 chains of the GBM. Despite the improvement in the progression of the disease with RAS blockade, Alport syndrome remains the most frequent monogenetic cause of glomerular disease leading to end-stage renal disease.[14] A preclinical proof of concept trial showed that establishing normal *Col4α3* expression in adulthood can considerably prolong survival in *Col4a3* −/− Alport mice.[15] In addition, there is new evidence from genetic manipulation in Alport mice that filtered albumin is indeed injurious for podocytes and/or tubular epithelial cells, thereby contributing to the progression of disease (unpublished, reported by Dr Jeff Miner). These data further support the use of antiproteinuric therapies such as RAS blockade in patients with Alport syndrome and perhaps in other genetic, proteinuric glomerular diseases as well.

INSIGHTS FROM GENETICS

Identification of genetic mutations in hereditary and sporadic FSGS, and the nephrotic syndrome has greatly increased since the advent of next-generation sequencing techniques.[16,17] Yet, currently only approximately 30% of suspected genetic FSGS cases can be explained by known affected genes, whereas in 70% the etiology remains

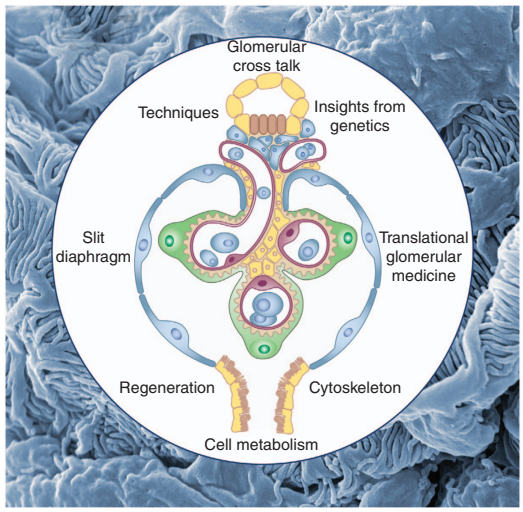

Figure 1 | Session themes of the 2014 International Podocyte Conference. Aiming to understand the integrated function of glomerular cell function.

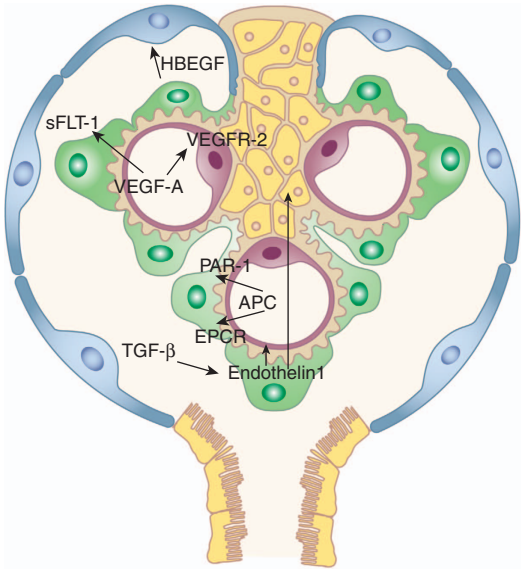

Figure 2 | Novel pathways of glomerular cross talk. Several important pathways of para- and autocrine cross talk within Bowman's capsule have been established during recent years. VEGF-A is produced by podocytes and is essential to maintain endothelial integrity acting via VEGFR-2. On the other hand, there is an autocrine loop being operated via sFLT1 (or soluble VEGFR-1), which maintains the actin cytoskeleton of the podocyte. During inflammatory diseases, i.e. RPGN, podocytes start to secrete HBEGF, which stimulates activation and proliferation of parietal epithelial cells. TGF-ß induces endothelin-1 formation in podocytes, which leads to endothelial dysfunction in diabetic nephropathy. On the other hand, endothelin-1 also leads to mesangial cell proliferation and sclerosis and in addition also has injurious effects on podocytes themselves. The thrombomodulin-dependent formation of APC in endothelial cells protects podocytes via the PAR-1 and EPCR. Disruption of this pathway may lead to podocyte apoptosis and might constitute a driving force for diabetic nephropathy. APC, activated protein C; EPCR, endothelial protein C receptor; HBEGF, heparin-binding EGF-like growth factor; PAR1, protease-activated receptor1; RPGN, rapid progressive glomerulonephritis; TGF-ß, transforming growth factor-beta; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.