A new urinary space within the glomerulus? 3-D reconstruction from Electron micrograph reveals a significant restrictive sub-podocyte space.

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The current understanding of glomerular ultra-filtration suggests there is little resistance to flow after the filtrate has traversed the glomerular filtration barrier (GFB) since it has direct access to Bowman's space (BS).

We have reconstructed podocytes and underlying basement membrane (GBM) in three dimensions (3D) using electron micrographs of ultra-thin (100nm) serial sections of rat and human kidney. Micrographs of serial sections were aligned and analysed using Adobe photoshop/NIH image and 3D models made. An initial survey of the GFB in rats revealed that while the majority of filtration slits between foot processes open directly into the BS (66±7%, range 20–80%), the remainder open into the space between the podocyte cell body and GBM. Full reconstruction of podocyte and sub-podocyte space (SPS) showed narrow pores (0.6±0.2_m diameter, n=5) or channels (0.16±0.03_m wide, n=6) connecting the SPS to BS. These pores/channels lie between neighbouring podocytes. A preliminary examination of human podocytes reveals similar results. The patent area of the pores/channels connecting SPS to BS is 0.25-0.5% of the GBM area draining into the SPS. The narrow exits from the SPS therefore form a downstream restriction to ultra-filtrate formation over a significant area of GFB and increase the path length that filtrate is forced to traverse before BS is reached.

The functional significance of this newly discovered urinary space has yet to be determined, however some intriguing possibilities present themselves. We speculate that the podocytes themselves may be able to influence single nephron GFR since an assessment of the relevant Starling forces shows that re-absorption into the blood capillaries is possible if the pressure within the SPS is only modestly increased above that in BS. Such changes in SPS pressure would produce backwashing of the GFB (cleaning the filter) and enable podocyte derived proteins (eg Ang I or VEGF) to reach neighbouring receptor bearing endothelial cells.

We submit that the current understanding of glomerular micro-anatomy/physiology derived from 50 years of EM and physiological study requires re-evaluation.

Commentary by John Feehally

The great thing about anatomy is that it seems unlikely it will change, or at least unlikely that major discoveries will surprise us. Nephrologists live their lives under the imposed thinking of standard medical school teaching about the structure and function of the glomerulus, content with the simple ideas they learnt early on about how the glomerulus goes about its business, the structure of the glomerular filtration barrier, and the straightforward notions of water and solute flux which assist our workaday needs. Over the last 30 years we have got more and more excited about the lively activity of the mesangial cells and the range of its repertoire, and the podocyte has turned out to be much mote interesting than it appeared when it was seen as little more than an end stage cell with a scaffolding role, but nothing has shaken our basic understanding of glomerular structure and function.

So what a surprise to discover all is not as it had seemed. And all the more remarkable that the discovery should come about by painstaking 3D reconstruction of those electron micrographs which we had all seen again and again. So there is a space we had never heard of, which we have learnt to call the subpodocyte space, and since the entries and exits to that space are remarkably restricted the anatomy goes on to beg all sorts of questions about given truths about pressure and flux across filtration barrier which require is to reconsider the truth as we knew it.

Things will never be the same again.