Bloody cyclists

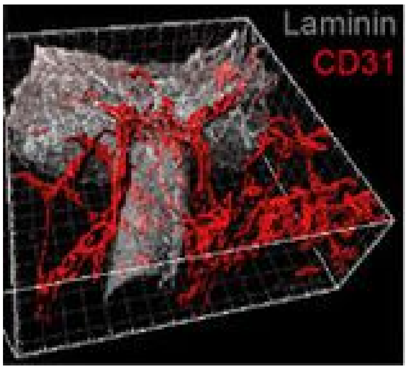
As regular readers of this blog will know, one of the main interests of this lab is understanding how cells organize themselves to make organs, both for the sake of the knowledge itself and also for what it can tell us about how to make organs artificially, 'to order'. David Munro, a 2nd-year PhD student in the lab, has just published some of his work on the way that one tissue in a growing organ can use another as a guide to what shape it should make (see 'links' below for a link to the full paper).

The internal structure of the kidney is dominated by tubes; vessels to carry blood, and tubules of various types to carry the liquid that will emerge as urine. Depending on how one chooses to count, there are between 3 and 20 million tubes of various types in each human kidney, all arranged in intricate and important relationships with one another. How does the kidney get everything in the right place?

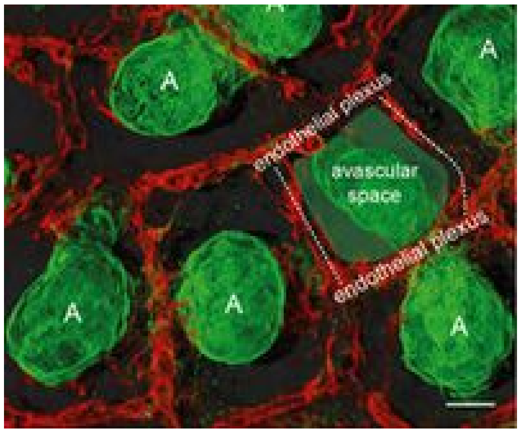
It has been known for many years (well over a century) that the first tube system to develop in the kidney is the urine collecting duct system. This enters the kidney-forming area of the embryo as a tube (the 'ureteric bud'), and the tube branches and branches again, many times, as it grows to make a tree. It has also been known for about as long that the tubules called nephrons, which do most of the business of making urine, form near the tips of the growing tree and connect to its branches. Thus the anatomy of the tree determines the position of the nephrons that connect to it.

So far, so good, but how about the blood vessels that bring blood to the filters (glomeruli) at the free ends of the nephrons so that it can be filtered and have its wastes passed out as urine? How do they find the nephrons? In 1992, Georg Breier and colleagues showed that the parts of the nephrons destined to make filtration apparatus secrete a protein called VEGF, which attracts any blood vessels in the vicinity to them. This suggested a kind of hierarchy, in which the development of the collecting duct system positions the nephrons, and the nephrons shape the blood system by attracting branches to themselves. This explanation was missing one detail, though – why were there vessels in the rough vicinity of nephrons in the first place? Do they wander randomly in the hope that they would end up somewhere close enough to a nephron to be useful, or are they placed roughly-accurately to begin with so that only fine details depend on signalling from nephrons? This is the question that David set out to answer.

Using advanced microscopy techniques to examine intact, three-dimensional mouse embryonic kidney rudiments of different ages, David showed that the early blood vessels take their cue from the crowing collecting duct system, and the cells that surround its tips. Very early, when the future

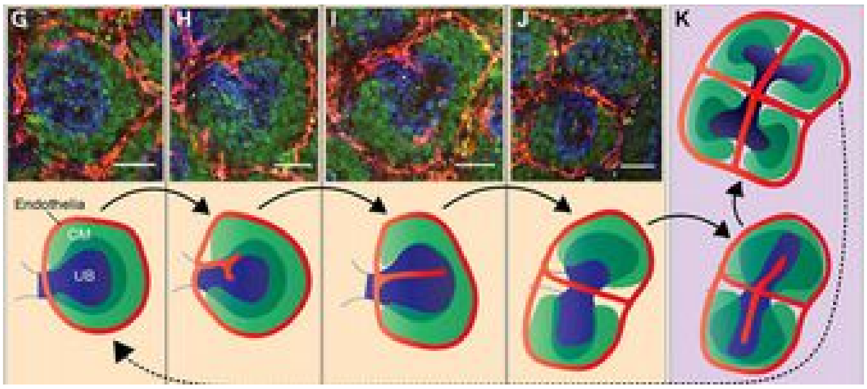


collecting duct system (shown light grey in the image to the left) has branched only once, tiny blood vessels have already grown along its trunk. Furthermore, they have formed a ring-like 'cuff' just under the branching point, and a few pioneering sprouts are heading off towards the point at which branches diverge. As development proceeds, these pioneering sprouts join up over the branch and send new branches to follow along the new branches as they extend. When the new branches branch, the blood vessels form new cuffs below the new branching point, and again send pioneering sprouts up and over to run through the 'Y' of the branch. In the figure to the right, in which we are looking down at branches coming up at us our of the screen (as a bird flying over a tree might see its branches when looking down), it is possible to see two branches between which new blood vessel



sprouts have already grown and joined up. To the bottom left of the diagram, the older branching point between the tips 'A' now have a quite thick vessel between them.

This sequence of events repeats again and again as the collecting duct system branches, the vessels always making a cuff below the branch and sending new sprouts to cross the 'Y'. This kind of thing is hard to explain on a two-dimensional screen, but the figure on the next page (from David's paper) is an attempt.



David's cartoon diagram of the cycle of vessel growth, sprouts growing from cuffs around existing branches of the collecting duct, to cross the Y of their next branching point, and join to make a new cuff, and so on.

The vessels that do this enter the kidney in the first place by branching off the main vasculature of the developing embryo (see the paper for more details). This means that the vessels are already carrying blood cells, a fact that David proved by using specific stains for them.

His work has shown a hitherto unsuspected growth cycle in renal blood vessels, a repeating sequence of sprout extension, joining and cuff formation patterned by, and presumably controlled by, the underlying collecting duct system. This explains why vessels are always close to the collecting ducts and therefore close to the nephrons that form near those ducts. It is not random at all – it is arranged with some precision.

On the day this paper was published, David submitted the second paper of his PhD (so far), on the search for a molecular mechanism that controls the blood vessel cycle. No doubt an account will appear in this blog when the paper actually comes out.

Jamie Davies

Edinburgh

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Links:

David Munro's paper (topic of this blog): https://www.nature.com/articles/s41598-017-03808-4

Georg Breier's 1992 paper on VEGF: http://dev.biologists.org/content/114/2/521.long