The creative power of self-loathing

Don't worry, this is not going to be psycho-babble: it's the story of another modest advance in our understanding of how our organs built themselves in the months before we were born (see the 'links' section for the published paper).

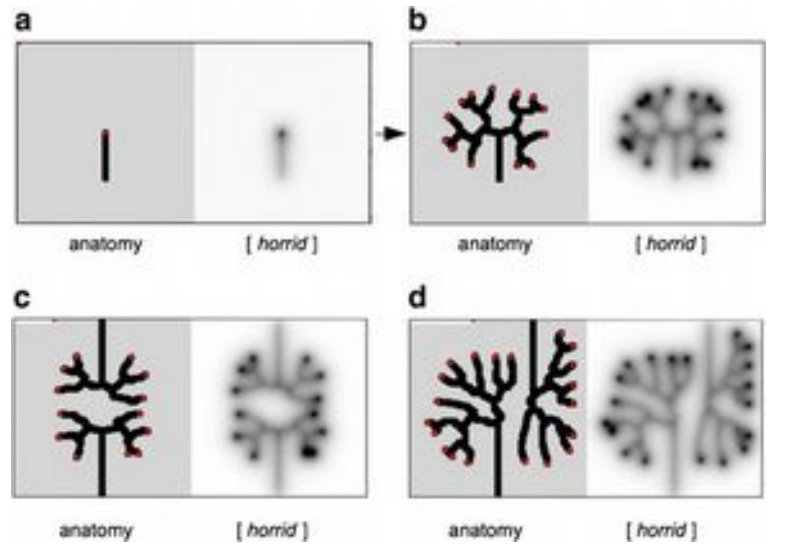
The anatomies of many of our internal organs are based on trees of one sort or another. The lungs are dominated by the tree-like branching system of bronchi and bronchioles that carry air to the alveoli, the pancreas is arranged around a tree of ducts to carry digestive enzymes to the gut, the salivary and mammary glands are built around the tree-like tubes that carry their secretions, and the kidney is arranged around a highly branched urine collecting duct system. The shapes of these trees are highly efficient, in terms of spreading out to serve as much organ volume as possible with minimum length for secretions (or air, in the case of lung) to travel.

How do the tree branches know in what direction to grow? It is clearly not the case that they read some kind of detailed genetic instruction set that tells them exactly where to go. The branch systems of identical twins are not identical in their find detail (nor are their fingerprints, incidentally, but that's another story); large animals like humans can make much larger and more branched tree systems than small animals like mouse, but they so not have larger genomes. More importantly, if one grows organs under strange constraints in culture, they still make trees that are appropriate for the space they have to fill. Tree growing is therefore, in some sense, autonomous and adaptive.

Working on kidney, I thought for a long time that the spreading of branches depended on signals from the cells through which the branches were growing, and indeed suggested this in a number of reviews in the 1990s. We knew (indeed, we helped to discover) that cells of the kidney that had not yet had a branch come near them secreted a signalling molecule (GDNF) that encourages branch growth. We also knew that a short-range signal from the branches made these cells, once branches were very near, go on to be something else that no longer made GDNF. If therefore made sense to assume that the branches extended towards GDNF and that would always take them out to the areas least-well served already, and would therefore ensure the spreading of the tree. Great! Then Sanjay Nigam and his colleagues showed that it was possible to culture the branching system on its own, with no other cells about and it still branched. Back, as they say, to the drawing board...

A completely different way of ensuring branching would be through the use of negative instead of positive signals. Imagine that the tree system wants to grow, but that each branch secretes a molecule – let's call it 'horrid' – that is repellent to branches. Clearly if the concentration is too high, nothing will grow, but if horrid can spread away well enough, then some growth may still be possible. Around each branch will be a 'field' of horrid, the local concentration of which will depend on how much is coming from that branch and how much from any branches nearby. If branches always grow in the direction of lowest horrid concentration, then perhaps this system would be enough to ensure a nicely spread tree.

To test the idea, I wrote a simple computer model in which branches knew nothing about tree anatomy; they just secreted a diffusible horrid, and grew in the direction at which its local concentration was lowest. Pleasingly, the result was a nicely spread tree on the computer screen:



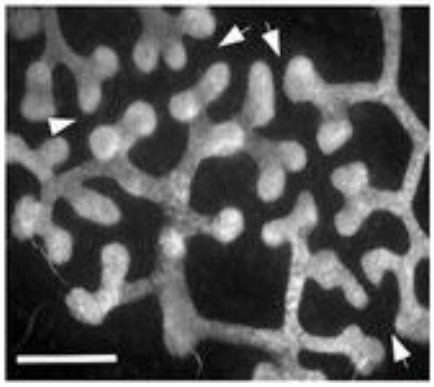
The computer model: (a,b) a simple 'trunk' that secretes horrid (the shading in the whiter panels) will branch to produce a well-spread tree. All of the branch angles emerge from the action of self-repulsion and they are not programmed in. (c,d) show attempted collisions in the computer model, and the way in which trees prefer to become distorted than to make contact.

The implication of this idea is that branches will avoid one another even if placed on a head-on collision course. Again, this idea could be set up in the computer, and it worked; trees became distorted rather than colliding. It was time to try this for real.

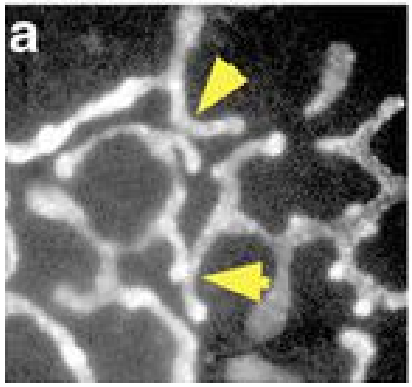
As I have mentioned in previous blog articles, kidney rudiments can be grown very well in culture and, with a good microscope and a steady enough hand, it is possible to set up pairs of kidneys so

that their trees face each other and, if each developed normally, they would collide. When I did this (and for once these experiments really were mostly done by me, with my own hands, rather than by the post-docs and students who work with me), the tips of the branches bent away from one another to avoid colliding. It looked as if they really did not like one another!

This attempted collision culture system turned out to be useful to trying to chase the mechanism by which the branch tips detect one another. If, as the model suggested, they secrete something they hate, then treating an attempted-collision culture with a drug that blocks the action of that something ought to result in collisions. Following this idea, for the next few weeks I made a thorough nuisance of myself cadging small samples of useful drugs, that block whole families of signalling pathways, from colleagues. One drug, that blocked a family of signalling systems, caused the trees to grow very quickly and collide. A steady process of using drugs and other molecules that blocked smaller and smaller sub-groups of that family finally identified BMP7 as the molecule that is made by branches, and which is apparently repellent to them.



Real trees avoid collisions...



… unless BMP7 signalling is blocked.

It seems then, in kidneys at least, that one important mechanism for spreading the tree is simple self-loathing: like British people sitting on an underground train, each branch positions itself to maximize its distance from all others. It will be interesting to see if other organs do this too.

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Links:

The paper: http://bmcdevbiol.biomedcentral.com/articles/10.1186/s12861-014-0035-8