Huseyin finds a new target in the battle against renal cystic disease

Autosomal dominant polycystic kidney disease, usually abbreviated to ADPKD, is the most common lethal single-gene disease in humans. It causes kidney to develop large internal cysts, the expansion of which crushes normal kidney tissue and eventually leads to kidney failure, usually in late middle-age. Once this has happened, a someone suffering from the disease needs to go on to dialysis or, if they are lucky, to receive a transplant. There are no good treatments for ADPKD; the best available, Tolvaptan, has side effects many patients find intolerable, and only slows disease progression anyway; it does not solve the problem.

Most cases of ADPKD arise from mutation of one of two genes, *PKD1* or *PKD2*, that encode proteins that form a complex that forms a regulated channel allowing calcium ions to enter the cell. This is important, because cellular calcium ions repress the activity of adenyl cyclase in making cyclic AMP (cAMP), and excess cAMP would drive cyst-making behaviour. The basis of using Tolvaptan is that it reduces cAMP levels in some kidney cells, and thus protects them to some extent from becoming cystic.

This is not really a disease-focused lab, but a few years ago a talented young student, Hüseyin Gül came over from Türkiye to do a PhD in my group, and wanted to work on ADPKD. The focus of his question was the reversibility of cysts, and I may write about this in a later blog post. The starting point for this blog is that his work involved making a culture model of cyst formation in kidneys. The model he used was not itself novel – it has been used several times before – but it fitted very well with general work in this lab. Hüseyin took kidney rudiments from mouse embryos and cultured them either in normal media or media supplemented with drugs that drive up the level of cAMP signalling, elevation of which is, as mentioned above, a fundamental feature of ADPKD. The kidneys in normal media grew normally with no cysts, while those in cAMP-elevating drugs developed cysts. Examples can be seen in the figure over the page.

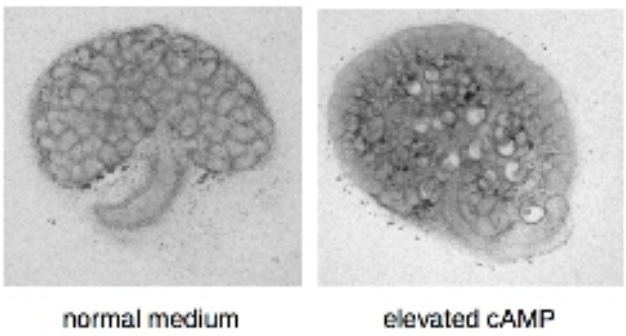

Figure 1: Mouse embryonic kidneys grown in standard medium, and the same medium supplemented with a drug (forskolin) that elevates cAMP. The presence of very enlarged tubules ('cysts') in the drug-treated example is obvious.

While Hüseyin was setting this up, I was doing some routine checking on the Guide to Pharmacology database (www.guidetopharmacology.org) we run on behalf of the International Union of Basic and Clinical Pharmacology and the British Pharmacological Society. There are formal quality control processes for this database, but I supplement this with a very simple additional check. Every few weeks, I pick an entry to the database at random and do my own literature search on the topic, to check that the database contains all of the relevant information I can find in the research literature. Entirely at random, I picked a human protein TRPM3, about which I knew absolutely nothing, and decided to do a literature search on it. In the course of this search, I discovered something intriguing; TRPM3 has been shown to associate with the protein encoded by PKD2. The group who showed this did not seem to show any interest in ADPKD so did not follow up whether TRPM3 might have anything to do with that disease. I read further, and found that TRPM3 forms calcium channels either as a complex of multiple TRPM3 molecules or as a complex of TRPM3 and other members of its family. PKD2 is a member of the same broad family of proteins as TRPM3. And conveniently, TRPM3 is the target of several drugs (that is why it was in the Guide to Pharmacology in the first place). I therefore showed all of this to Hüseyin, and asked if he would be willing to test the effects of activating or blocking TRPM3 on cyst development in his cultured kidneys.

To cut a long story short, drugs that inhibit TRPM3 make cyst formation worse. This makes intuitive sense, because these drugs would, by blocking TRPM3's ability to bring calcium into the cell, reduce inhibition of adenyl cyclase. More excitingly, drugs that activate TRPM3 greatly reduce or block the growth of cysts. The original data supporting this summary can be found in Hüseyin's paper (see Links at the end of this blog).

We had only two drugs that activated TRPM3 and inhibited cyst growth. One of them, CIM0216, is a research-only compound, not approved in patients. The other, nifedipine, is approved in patients but it affects more than just TRPM3. Importantly, as well as activating the TRPM3 calcium channel, it inactivates L-type calcium channels, which have a huge effect on calcium in cells. This second effect made no difference in Hüseyin's embryo-derived model, because young embryonic kidneys do not have L-type channels. Adult kidneys, though, do have L-type channels so nifedipine would probably end up making things worse, not better, by shutting off calcium flow through L-type channels while activating it through TRPM3.

The most optimistic view of Hüseyin's work is that he has found a promising new drug target that might repress cyst development in patients with ADPKD. But targeting TRPM3 in patients for this purpose will need a specific drug, not nifedipine. It is important to note, though, that all of our evidence has been obtained from mouse kidneys in culture. We need to find out whether it works in human kidney organoids in culture: if the TRPM3 activation trick does not work in human, there is no point in going on. If it does, then at some point it will need to be tested in animal models. That is not work for us – we do not do experiments in live animals – but a different lab that does may be interesting in collaborating or in testing the idea independently.

Links

- Hüseyin's paper: https://pubmed.ncbi.nlm.nih.gov/39922884/