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Sonia Fernandez

A ‘magic bullet’ for polycystic kidney disease in the making

Polycystic kidney disease (PKD) is a debilitating hereditary condition in which fluid-filled sacs form and proliferate in the kidneys. Over time, the painful, growing cysts rob the organs of their function, often leading to dialysis in advanced cases There is currently no cure.

Researchers at UC Santa Barbara, however, have proposed a cyst-targeted therapy that could interrupt the runaway growth of these sacs by leveraging the target specificity of the right monoclonal antibodies — lab-made proteins that are used in immunotherapy.

“The cysts just keep growing endlessly,” said UCSB biologist Thomas Weimbs, senior author of the study published in the journal Cell Reports Medicine. “And we want to stop them. So we need to get a drug into these cysts that will make them stop.”

This research was funded in part by the National Institutes of Health and the U.S. Department of Defense.

Interrupting a runaway process

There are a variety of small-molecule drugs that promise to rein in the growth of these sacs. However, the only currently available drug that shows some effectiveness at slowing the progression of the disease comes with many side

effects and toxicities to the tissues in and around the kidneys, Weimbs said. Lab-grown therapeutic antibodies are an alternative treatment that have the benefit of specificity, but the one now produced almost exclusively, immunoglobulin G (IgG), is too large to gain access into the cysts.

“They’re very successful for cancer therapy,” Weimbs said. “But IgG antibodies never cross the cell layers and they can never make it inside the cysts.” And that’s important, he added, because inside the cyst — a pocket of tissue lined with epithelial cells — is where the action is.

“Many of the cyst-lining cells actually make growth factors and they secrete them into the cyst fluid,” he explained. “And these growth factors then bind back to the same cells or to neighboring cells and continue to stimulate themselves and each other. So it’s like a never-ending scheme in which the cells just keep activating themselves and other cells in there. Our premise was that if you block either the growth factor or the receptor for the growth factor, you should be able to stop this constant activation of the cells.”

Enter dimeric immunoglobulin A (dIgA), a monoclonal antibody with the ability to cross epithelial membranes. In nature, dIgA is an immune protein that is secreted into tears, saliva and mucus as the first line of defense against pathogens. By binding to polymeric immunoglobulin receptors found on epithelial cells, Weimbs and team reasoned in a 2015 paper, the antibodies take a one-way trip through the membrane into the kidney cysts, where they can target specific receptors to interrupt the cycle that leads to the unchecked growth of the cysts.

This paper continues that line of investigation, and proves the therapeutic efficacy of the strategy by targeting a driver of cyst progression, the cell mesenchymal-epithelial transition (cMET) receptor.

The researchers first engineered the antibody protein, which involved manipulating the IgG’s DNA sequence to “give it a different backbone” that would turn it into a dIgA antibody. Next they tested the resulting proteins to confirm that they work against the target receptor, then tested it in mouse models. They found that the administered antibody did indeed travel into the cysts and stayed there.

“The next question was, could it actually block that particular growth factor receptor,” Weimbs said. Their results indicated that cMET activity was inhibited, which in turn lowered the cell growth signals. Not only that, but according to the paper, the treatment appears also to have triggered a “dramatic onset of apoptosis (cell death) in cyst epithelial cells, but not in healthy renal tissue” with no apparent deleterious effects.

With the research still in preclinical stages, it will be quite a while before this treatment done to mice can be transferred to human beings, Weimbs noted. Future challenges for the team include finding partners that may have interest in PKD, and access to facilities and technology that could generate these and other potential antibodies to find the best ones, as well as finding other targets for the immunotherapy.

“In the literature there are dozens of growth factors that have been shown to be active in these cyst fluids,” Weimbs said. “So it would be a good idea to compare blocking of several different growth factors and several receptors, maybe side-by-side to see which is the most effective, and see if we can achieve slowing or reversal of the disease with any one of them. We can also combine different antibodies against different receptors at the same time. That would be the next step.”

Research in this paper was also conducted by Margaret F. Schimmel (lead author), Bryan C. Bourgeois, Alison K. Spindt, Sage A. Patel, Tiffany Chin, Gavin E. Cornick and Yuqi Lu at UCSB. Additional funding was also provided through gifts from the Amy P. Goldman Foundation and the Lillian Goldman Charitable Trust.

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Media Contact
Sonia Fernandez
Senior Science Writer
(805) 893-4765
sonia.fernandez@ucsb.edu

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