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Treatment of Kidneys from Nephritis by Peptide

Joseph Khan*

Department of Nephrology, Centre Hospitalier Le Mans, Avenue Roubillard, Le Mans, France

Description

A synthetic peptide appears to directly disrupt the destructive inflammation that occurs in nephritis, enabling the kidneys to better recover and maintain their important functions.

Whether they gave the peptide body-wide or delivered it directly to the kidneys, it reduced the movement of immune cells into the kidneys, resolved inflammation and damage and improved kidney function, without increasing blood pressure. Things like a serious infection or injury, and diseases like uncontrolled hypertension and diabetes, can cause acute or chronic nephritis, which affects both kidneys and the million filtering units in each. Particularly when it's chronic, patients often wind up in kidney failure and on dialysis, which has basic scientists and physicians alike looking for better interventions.

In a model mimicking severe nephritis, which is essentially 100 percent lethal to the kidneys in humans and deadly to the mouse model, with treatment there was instead an 80 percent survival of the mice. At later stages of the disease, low doses of the peptide also reduced the level of T-cells, drivers of the immune response and inflammation, moving into the area. In fact, levels were essentially normal. The peptide appears to actually improve the general condition of the kidney over time. The peptide, which has already been tested in Europe in patients with acute lung injury, like pneumonia or trauma, and is being pursued in lung transplant patients as well, holds promise for a targeted therapy for acute nephritis. Reversed inflammation in the kidney during the course of nephritis showed that it was effective and shows local effect within the kidney itself.

Current therapies, like corticoid steroids, generally suppress the immune response, leaving patients at risk for infection and even cancer. The TIP peptide Lucas developed is a synthetic version of the tip of tumor necrosis factor, or TNF, which as its name implies, is known to target cancer. But TNF is also a primary instigator of destructive inflammation in nephritis. In a mouse model of nephritis, watched immune cells arrive in response to an attack on the kidney in this case a toxin which in turn generated a lot of TNF. TNF then activated two main inflammation-promoting pathways in the endothelial cells that line the million kidney filtering units, called glomeruli, in each kidney as well as the podocytes, cells that wrap around the tiny capillaries of the filtering units. The most important of the inflammation-promoting pathways activated by TNF in this case are p38 MAP kinase along with NF-kB.

TNF also decreased production of things like nitric oxide, a powerful blood vessel dilator that could help the kidneys recover, as well as prostaglandin E2, which can suppress the immune response and inflammation. This is how high levels of TNF are bad for us, and the consequence of this is now you get an increased protein in your urine and you will get increased renal inflammation. Directly suppressing TNF, that might not be a good idea because of its important roles in fighting infections and other invaders, which is already a concern for current treatments. Factors that interfere with the deleterious TNF signaling, which induces the profound inflammation in the kidneys, without interfering with TNF's defense role against bacteria.

The peptide directly activates ENaC-alpha, a subunit of natural body channels which mediate sodium uptake and play a role in fluid movement. While the peptide's activation of ENC-alpha in the lungs is a good thing in pneumonia where fluid literally interferes with breathing, the investigators were concerned that activating ENaC-alpha in the kidneys might disturb normal sodium retention, which is important to the kidney's role in blood pressure regulation. They found instead that the TIP peptide delivered directly to the kidneys not only reduced inflammation but actually decreased blood pressure, even in the face of a high-salt diet, and without interfering with the infection-fighting role of TNF.

Inflammation of the kidneys filtering units, called glomerulonephritis, is responsible for about 10-20 percent of the extensive kidney damage patients experience, although the affected pathway is common to many forms of progressive kidney damage. Glomerular filtration goes down the drain, then the body weight increases because of retain of more urine. TNF is a crucial mediator of this pathology. TNF and another pro-inflammatory substance called interleukin 1, produce products like reactive oxygen species that damage both the filters and the elastic cells that wrap around their exterior. Activating ENaC-alpha with his peptide can help eliminate deadly fluid buildup in the lungs that can occur in pneumonia. This is a very different approach from the work in the lungs.

In the kidneys, the peptide directly interferes with a major cause of the problem which is p38, and it is known to play an important role in

***Address for Correspondence:** Joseph Khan, Department of Nephrology, Centre Hospitalier Le Mans, Avenue Roubillard, Le Mans, France; E-mail: Josephk@gmail.com*

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cells that line blood vessels and the heart, and like those lining the glomeruli.

There are about a million filtering units, called nephrons, in each kidney that remove waste, acid and excess fluid from the blood, which get excreted into the urine. The glomerulus, a cluster of blood vessels inside the nephrons, function as the actual filter.

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