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Breakdown of kidney's ability to clean its own filters likely causes disease

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The kidney actively cleans its most selective filter to keep it from clogging with blood proteins, scientists from Washington University School of Medicine in St. Louis reveal in a new study. Researchers showed that breakdown of this self-cleaning feature can make kidneys more vulnerable to dysfunction and disease.

"We speculate that defects of this clearance mechanism can leave things on the filter that can damage it," says senior author Andrey Shaw, M.D., Emil R. Unanue Professor of Immunobiology in Pathology and Immunology. "This could include autoimmune antibodies that mistakenly target the body's own tissues like those that occur in the disease lupus."

The study appears in the Jan. 22 *Proceedings of the National Academy of Sciences*.

Despite extensive knowledge of the structure of the kidney, several scientific controversies linger over how the organ does its complicated and essential job of filtering wastes from the blood for disposal without simultaneously discarding too much water or key blood proteins in the urine. Understanding how these tricky tasks are accomplished is essential to developing new treatments for kidney disease and renal failure, which are among the top ten causes of death in the United States.

Like many mechanical filtering systems, the kidney passes the blood through a series of progressively finer screens. After passing through a

structure known as the glomerular basement membrane (GBM), fluid and serum proteins must finally pass through the most selective filter of the kidney, which is comprised of specialized epithelial cells called podocytes. These cells form a web-like barrier to the passage of large serum proteins into the urine.

"The kidney screens 150 to 200 liters of blood daily, and we were curious as to how the kidney keeps the filter from clogging up," says first author Shreeram Akilesh, an M.D./Ph.D. student. "The two most common blood serum and plasma proteins are albumin, which helps regulate blood volume and convey a number of different substances around the body, and immunoglobin G (IgG), a type of immune system antibody. Because they're so common, we figured they would be among the most likely to get stuck on the filter, and set out to look for proteins that help clear them."

Researchers looked for proteins made in podocytes that could bind to albumin and IgG, reasoning that such proteins likely provide the "handles" the podocytes need to grab proteins and clear them from the filter.

A protein known as FcRn was high on the list of likely suspects. Akilesh had studied FcRn previously in the laboratory of coauthor Derry C. Roopenian, Ph.D., professor at the Jackson Laboratory in Bar Harbor, Maine. Prior research there and in other laboratories had revealed that FcRn binds to both IgG and albumin and is present in human podocytes.

After confirming that the FcRn protein also is made in mouse podocytes, scientists then asked if FcRn was responsible for clearing IgG antibody from the filter. To do this, they measured the retention of a radioactive tracer in the kidneys of normal mice and in mice where the gene for FcRn had been disabled. Mice lacking FcRn had difficulty clearing antibody from the kidney.

When researchers studied the mice lacking FcRn for longer periods of time, they saw evidence that antibodies were accumulating in the kidney.

In another experiment, researchers gave the mice injections of large quantities of protein to saturate the clearance system. They followed those injections with what would normally have been a harmlessly small dose of an antibody potentially toxic to the kidney. The mice developed kidney damage as a result. Researchers believe this was because they couldn't clear the toxic antibody from the GBM quickly enough.

"This is the first clear demonstration that the filter system in the kidney isn't just a passive mechanical filter, it's actually involved in its own maintenance," says Akilesh. "It also provides us with a nice mechanism for explaining how the normal function of this filter may be breaking down in ways that leads to kidney disease and damage."

To follow up, Shaw plans to look for other podocyte proteins involved in filter clearance.

Source: Washington University School of Medicine