Bone marrow-derived cells are source of key kidney disease biomarker SuPAR

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Jochen Reiser, MD, PhD, Professor and chairperson of the Department of Internal Medicine at Rush University Medical Center leads research into chronic kidney disease Credit: Rush PhotoGroup

A protein known as suPAR has been identified in recent years as both a reliable marker for chronic kidney disease and a pathogen of the often deadly condition. Its place of origin in the human body, however, has been a mystery—until now.

In study results published Dec. 12 in the journal *Nature Medicine*, a research team announced they have identified a type of immature myeloid cell, located in the bone marrow, as the source of abnormal levels of suPAR.

"These immature myeloid cells appear as a main source of circulating suPAR," says Jochen Reiser, MD, PhD, principal investigator and senior author of the study presented in *Nature Medicine*, who has been working on solving the mysteries of suPAR for more than a decade. Reiser is Ralph C. Brown, MD, Professor and chairperson of the Department of Internal Medicine at Rush University Medical Center.

At least 10 percent of adults in the United States—about 25 million people—have chronic kidney disease, according to the U.S. Centers for Disease Control and Prevention. More than 48,000 of them die every year, and Medicare alone spends about $49 billion on medical care for its patients with chronic and end-stage kidney disease every year. Because kidney disease tends to have no early symptoms, most people who have the disease don't know it until serious damage has been done, and may go untreated.

Elevated levels of creatinine in the blood—which indicates how well the kidneys are filtering waste - and high protein levels in urine - a condition called proteinuria—can alert clinicians that an individual is suffering from chronic kidney disease. However, by the time those biomarkers show up, the disease is underway and the kidneys have being damaged.

The discovery that elevated suPAR levels are a reliable predictor of

future chronic kidney disease therefore was exciting news , because it signaled the approach of a day when clinicians will be able to track their patients' suPAR levels just as they now track cholesterol levels—and to intervene to control impending kidney disease when suPAR levels rise.

Everyone has urokinase plasminogen activator receptor (uPAR), a healthy molecule "tethered" in place to various types of cells. It's the soluble variety, circulating in the blood stream, suPAR, that damages the kidneys.

Establishing suPAR as a marker of kidney disease was just the beginning, though.

One of Reiser's particular focuses in kidney research is a chronic, serious condition called focal segmental glomerulosclerosis (FSGS), which scars the kidneys and eventually destroys them. The disease often comes back after transplantation of a kidney, a condition called recurrence. His research with FSGS has expanded into more general findings about kidney disease more than once.

In two papers published in *Nature Medicine* in 2008 and 2011, Reiser's team showed that uPAR and its soluble form suPAR may be causative for FSGS. In 2015, Reiser and colleagues published work in the *New England Journal of Medicine* that showed that circulating suPAR associates with future chronic kidney disease in general, likely by delivering a "systemic insult" to these workhorse organs.

"SuPAR is not just a biomarker; it may also be a cause of the disease," Reiser says. That finding was "a game changer. You could predict new disease in people that by any available test still had normal kidney function."

At that point, identifying suPAR's cellular origins became critical. This

knowledge, the Nature Medicine paper states, is "one essential step" toward developing an effective treatment for this devastating disease - "hopefully sooner than later," says Eunsil Hahm, PhD, assistant professor of medicine at Rush and first author on the study.

Myeloid cells are one of three main types of blood cells. The role of bone marrow immature myeloid cells in the manufacture of suPAR was surprising, because "these cells were not known to be doing anything except maturing," and because bone marrow had not previously been linked to kidney function, Reiser explains.

Nevertheless, Hahm adds, it appears that "these cells are producing high amounts of suPAR, which becomes the mediator that communicates between the immune system and the kidney. At high levels, suPAR travels to the kidneys, causes a reaction, and takes the kidney down."

Researchers had deduced that circulating suPAR likely originates from outside the kidneys because clinicians see high levels of the molecule in patients that have received a new kidney after their own kidneys have been damaged by FSGS disease. Recurrence of FSGS can be as high as 30 percent in adults and even higher in children.

Not everyone develops kidney disease—not in the course of a life, nor after the receipt of a transplanted organ. In both cases, Reiser says, "The question was, what triggers the changes in the cells?" suPAR provides an answer and serves as the first identified bona fide circulating factor.

Reiser's team used a "humanized" mouse model that utilizes patients' peripheral blood stem cells to communicate signals to mouse bone marrow immature myeloid cells. These genetically modified animals serve as a transfer study system of human kidney disease and thus as a study aid to investigate the production and action of suPAR.

Early discoveries led researchers to home in on the hematopoietic system, the organs that produce the two kinds of blood cells, lymphoid and myeloid cells. Using mice bred to lack some types of lymphoid cells, among other features, researchers were able to show that those mice still had high levels of suPAR and proteinuria, indicating that lymphoid cells were not the perpetrators of kidney disease. At that point, the team began to focus on the myeloid cells, leading to their new findings.

Further research will be necessary to establish solid connections between the suPAR production site in mice and the human cell types, Reiser says. It also might be possible to establish a genetic link to the process that unleashes suPAR on a person's system. FSGS rates are high in the black population, for example, Hahm adds.

As for treatments, the paper states, "Stem cell transplantation may prove to be a viable approach to treat diseases such as suPAR-associated kidney disease."

"The benefit of knowing what we know about suPAR is that it will allow for much better risk stratification," Reiser says. "If a company has a new medicine for kidney disease they would want to test for suPAR, because it will tell you which patients are most vulnerable to the disease."

There is a lifestyle aspect to suPAR, Reiser notes; smoking and weight gain, for example, can contribute to elevated suPAR levels. "Bad habits increase the risk of kidney disease," he says.

While smoking cessation and losing weight can help bring suPAR levels down, as with cholesterol levels, adopting good habits has only limited benefits. SuPAR levels will likely require pharmacological intervention because "suPAR still won't go down to completely normal levels just because of a better lifestyle," Reiser says.

As to those immature myeloid cells that arise in bone marrow, they are more developed than stem cells, but have not grown into their final function as, for example, neutrophil white blood cells. The specific type of cells the researchers in the new Nature Medicine paper looked at, and identified as giving rise to suPAR, are bone marrow GR-1lo, Sca1+ immature myeloid cells.

In the *Nature Medicine* paper, titled, Bone marrow-derived immature myeloid cells are a main source of circulating suPAR contributing to proteinuric kidney disease, the suPAR researchers suggested that their discovery and their investigative approach owed much to the work of other investigators and might prove useful for researchers investigating other diseases that appear to arise spontaneously in certain individuals for no discernible reason.

More information: Bone marrow-derived immature myeloid cells are a main source of circulating suPAR contributing to proteinuric kidney disease, *Nature Medicine*, nature.com/articles/doi:10.1038/nm.4242

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