Protein offers new clue to cause and treatment for kidney disease

December 12 2010

University of Alabama at Birmingham researchers have pinpointed a protein that compromises the kidney's filtering ability, causing nephrotic syndrome, and demonstrated that a naturally occurring precursor of an acid in the body offers potential for treating some forms of the condition.

The research was published online Dec. 12 in Nature Medicine.

"This is a major breakthrough in understanding the development and treatment of kidney disease associated with proteinuria, the leakage of protein in the urine," said the study's lead author Sumant Singh Chugh, M.D., associate professor of medicine in the UAB Division of Nephrology.

Nephrotic syndrome is characterized by the presence of excessive protein in the urine, low blood-protein levels, high cholesterol, high triglycerides and swelling. Common causes include diabetic nephropathy, minimal change disease, focal and segmental glomerulosclerosis and membranous nephropathy. It also can be caused by infections, certain drugs, cancer, genetic disorders, immune disorders or diseases that affect multiple body systems including lupus, multiple myeloma and amyloidosis.

Chugh said his research team, studying transgenic rats, discovered that in some forms of nephrotic syndrome, a protein called Angiopoietin-like 4 is over-produced in specialized cells called podocytes. Podocytes are

found in the glomerular filter, which cleans the blood to produce urine. As a result of the over-production, the efficiency of this filter is compromised, resulting in the loss of blood proteins in the urine. When this dysfunction is severe, it causes nephrotic syndrome.

Chugh said the researchers also determined that the Angiopoietin-like 4 protein lacks the attachment of adequate amounts of sialic acid, a modified carbohydrate that affects the protein's adhesive properties. By feeding sialic acid precursor ManNAc to transgenic rats that over-produce Angiopoietin-like 4 in podocytes, the researchers were able to increase the amount of protein-bound sialic acid, and reduce the amount of protein leakage into the urine by more than 40 percent.

"These findings, at present, most directly relate to minimal change disease, a form of nephrotic syndrome commonly seen in children, but are also likely to be relevant to common causes of proteinuria and nephrotic syndrome in adults, including those with diabetes," Chugh said.

He added that this study is important because traditional forms of therapy, which include the use of glucocorticoids, for example prednisone, and other immunosuppressive drugs can have significant toxicity, especially after prolonged use or repeated cycles of treatment. However, sialic acid and ManNAc are naturally occurring substances in the body, and toxicity is likely to be limited. The investigators, he said, believe that relatively small doses of the sialic acid may be effective for nephrotic syndrome, since, unlike most other cells in the body, the target cell in the kidney does not divide under most conditions and is likely to accumulate these compounds even at low doses.

"The major known toxicity of sialic acid therapy observed by other investigators in a mouse model of the human muscle disease, hereditary inclusion body myopathy, was the development of ovarian cysts at very

high doses," Chugh said. "These doses are approximately 20-fold higher than those used to reduce proteinuria in rats in the current study; knowing that, we believe sialic acid repletion has potential in the future treatment of Minimal Change Disease and some other forms of nephrotic syndrome."

Provided by University of Alabama at Birmingham