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Findings provide new therapeutic route for rare kidney disease

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Scientists from the University of Leeds have discovered the mechanisms of a protein known to play an active part in the inherited kidney disorder, Dent's disease. The findings provide a new focus for future therapies for the disease, for which there is currently no cure.

Dent's disease is an extremely rare illness caused by a genetic mutation on the X chromosome. Affecting mostly men, its main symptom is kidney stones often followed by a deterioration of kidney function and in many cases chronic kidney failure. Treatment for the disease is focused on alleviating symptoms and can involve kidney transplant.

Scientists from the University's Faculty of Biological Sciences have uncovered the role of a transporter protein, called CLC-5, which is known to be faulty in many sufferers of Dent's disease.

Lead researcher Dr Jonathan Lippiat says, "This is a rare genetic disease so it's impossible to know the exact number of sufferers worldwide. Dent's disease could be the underlying cause of kidney stones or kidney failure for a larger number of people and it could be that a number of Dent's sufferers go undiagnosed. The faulty gene itself has been known about for quite a while, but there's been no concrete evidence about the function it fulfils. That's why we're excited by these findings - they provide us with a whole new area to examine in the search for therapies for Dent's disease."

In a research project supported by the Wellcome Trust, Dr Lippiat and

his team have discovered that CLC-5 facilitates a crucial function by allowing certain ions to pass through cell membranes so they can reach the places they are needed.

The kidneys filter our blood, removing waste, but minerals and hormones that we need to remain healthy need to be reabsorbed. In order for the cells in the kidney to reabsorb effectively, a process called endocytosis takes place to allow larger molecules to travel through the cell membrane.

In endocytosis, a compartment is created in the cell membrane for the molecule to enter. This compartment - or endosome - needs to be acidic in order for the process to work effectively. The research findings show that CLC-5 delivers protons into endosomes, which causes acidification to occur, so when it CLC-5 is faulty, endocytosis cannot take place effectively.

"If endocytosis can't take place we lose vital vitamins and hormones," says Dr Lippiat. "CLC-5 is actually part of a family of proteins, some of which are implicated in other diseases, so these findings could have important consequences when we're looking at the role of other proteins in the same family."

Provided by University of Leeds