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# New findings about the way cells work could lead to a test and therapy for kidney failure caused by E. coli

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Ever since the water supply in Walkerton, Ont., was contaminated by *E. coli* in 2000, Dr. Philip Marsden has been trying to figure out just how a toxin released by that particular strain of the bacteria causes kidney damage in children.

Now Dr. Marsden and his team based at St. Michael's Hospital and the University of Toronto, led by graduate student Tania Petruzziello-Pellegrini, together with an international team of collaborators, have made new discoveries about the basic workings of endothelial cells that could lead to a diagnostic test for the serious kidney disease known as hemolytic uremic syndrome (HUS) and a possible treatment.

Endothelial cells line the inside of blood vessels and are the cells most severely affected in HUS, one of the most common causes of sudden onset kidney failure in children.

His work took a sudden twist in May 2011, when an *E. coli* outbreak swept northern Germany and researchers discovered that a different strain of the bacteria was producing the identical toxin. This time the HUS mainly affected adults, especially women, and was associated with severe kidney failure and strokes.

Dr. Marsden's team extracted endothelial cells from healthy people and exposed them to the toxin in a culture dish. They discovered a biological

pathway never before known to have played a role in the development of HUS.

Specifically, they found that the toxin can increase the level of a chemokine, namely SDF-1, and its receptor, CXCR4. Chemokines are small secreted proteins that stimulate cells to move or migrate. CXCR4 was already known to stimulate the release and migration of the precursors of white blood cells from bone marrow, to change how blood vessels grow and to help the AIDS virus enter cells.

Dr. Marsden has found that too much communication between SDF-1 and CXCR4 molecules can also impact the development of HUS in animals and humans. His team made two important discoveries, published in The Journal of Clinical Investigation:

- injecting the drug plerixafor/AMD3100 (sold under the brand name Mozobil) into mice exposed to the *E. coli* toxin changed their survival rate and helped improve the HUS, suggesting future therapy options for humans. The drug blocks SDF-1 action on cells that express CXCR4. The drug is used to mobilize precursor stem cells from the bone marrow in some bone marrow transplant recipients during the treatment of non-Hodgkin lymphoma and multiple myeloma.
- blood tests taken from children with *E. coli* showed that those who went on to develop HUS had higher levels of the protein SDF-1—as much as four times higher than other children with *E. coli* who did not go on to develop HUS. This suggests that a blood test could be used to predict who is most likely to develop the potentially fatal HUS, meaning they could be monitored more closely.

Dr. Marsden, who is a nephrologist, said a safe water supply and clean

food supply chain is the most important step in preventing HUS caused by *E. coli*.

"If we can measure SDF-1 levels in real time during an *E. coli* outbreak and confirm these findings, then we have a strong case for a trial of plerixafor/AMD3100 in patients with toxin-producing *E. coli* to see if it prevents or improves cases of HUS," he said.

Provided by St. Michael's Hospital