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 Petruzzello-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

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