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Safe and effective therapy discovered for patients with protein-losing enteropathy

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Researchers at the Burnham Institute for Medical Research (Burnham Institute) have developed the first model to study intestinal protein leakage in mice, allowing the team to control and replicate both genetic deficiencies and environmental damages in an in vivo setting. Protein-losing enteropathy (PLE) encompasses conditions that involve the abnormal leakage of blood proteins into the digestive tract.

One type of PLE is observed in children who have undergone Fontan surgery, a procedure used to alleviate certain congenital heart defects. Half of post-Fontan patients who develop PLE die from this condition, due largely to therapeutic options that are inadequate and accompanied by serious side effects.

A study performed by the laboratory of Hudson Freeze, Ph.D., at the Burnham Institute has been published in the Journal of Clinical Investigation (JCI), describing both the science behind PLE and also a way to treat the disease that side steps some of the severe complications of current treatments.

Dr. Freeze's group, led by Lars Bode, Ph.D., identified commonalities in clinical observations of PLE patients that recognized several key features of PLE pathogenesis; in particular, it is episodic and its onset is often associated with viral infection and a proinflammatory state. The most intriguing commonality that the group observed in PLE patients is the specific loss of heparan sulfate (HS) from intestinal epithelial cells during PLE episodes. Importantly, the study revealed that loss of HS is a

key factor in promoting protein leakage and makes the intestine more susceptible to inflammation and increased hypertension. Co-author Simon Murch, M.D., University of Warwick, UK, first noticed the loss of intestinal cell HS in one of their previous collaborations.

“When heparan sulfate is missing, the inflammatory molecules pack a much greater punch and impact than when HS is there on the cell surface,” said Dr. Freeze, who is Professor and Co-Director of the Tumor Microenvironment Program at Burnham Institute.

The group had previously observed that soluble heparin compensates for loss of heparan sulfate and prevents protein leakage in vitro. However, long-term therapy with anticoagulant heparin has severe side effects, including bleeding, thrombocytopenia and osteoporosis. However, the study also revealed an alternative form of heparin as a potential therapy. By adapting well-established clinical assays to assess intestinal protein leakage in mice, Dr. Freeze’s team found that a heparin analog, 2,3-de-O-sulfated heparin, also prevented protein leakage both in vitro and in mice without causing bleeding. This compound exhibits greatly reduced anticoagulant activity, compared to unmodified heparin, which may mean that it can be used safely at much higher doses to treat PLE.

Source: Burnham Institute