Published in final edited form as:

N Engl J Med. 2008 July 31; 359(5): 526–528. doi:10.1056/NEJMcibr0803745.

Patching a Leaky Intestine

Wayne I. Lencer, M.D.

Department of Medicine, Children's Hospital Boston and Harvard Medical School, Boston

In patients with protein-losing enteropathy, the intestinal mucosa completely fails to function as a competent barrier separating the body from the outside world. Serum fluids and proteins quickly leak into the stool, causing diarrhea, hypoalbuminemia, and sometimes death. A recent study by Bode and colleagues¹ showed that the disease might be related to the loss of heparin sulfate proteins that are normally expressed on intestinal cells. Remarkably, the investigators also showed that the disease can be successfully treated with novel analogues of heparin sulfate.

For the intestine to efficiently absorb nutrient solutes, it first has to effectively separate the lamina propria from the intestinal lumen (Fig. 1A). Such barrier function is fully dictated by the single layer of surface epithelial cells that line this vast mucosal surface and, in particular, by the way these cells adhere to each other so as to seal the space between them. The proteins that join the membranes between adjacent cells form the so-called intercellular tight junctions, adherens junctions, and spot desmosomes. For most diffusible solutes, including the serum proteins, the nature of these junctions defines intestinal permeability.²

Intercellular junctions are actually highly dynamic, especially in the intestine, where surface epithelial cells are constantly regenerating and moving along the crypt–villus axis. They can be rapidly remodeled in response to the needs of nutrient absorption, mucosal inflammation, and wound repair. Some of the associated physiological stimuli have been established, including the release of the inflammatory cytokine tumor necrosis factor α (TNF- α) and the initiation of glucose absorption after meals. Other stimuli and the mechanisms through which they regulate intestinal-barrier function remain largely undefined.²

Bode et al. tested the idea that heparin sulfate proteins affect the intestinal barrier. Heparin sulfate proteins have large, heavily glycosylated, heparin-like extracellular domains fixed to the plasma membrane by the protein itself (the syndecans) or by attachment to a membrane glycolipid (the glypicans).³ Because the heparin-like domains can bind multiple proteins with diverse functions, heparin sulfate proteins can influence a variety of molecules, cell types, and processes. Although heparin sulfate proteins are not structural components of intercellular junctions, there is plenty of evidence that the loss of heparin sulfate proteins in the intestine is somehow related to protein-losing enteropathy¹ and, by inference, to defective intercellular junctions.

Bode et al. found that mice that were genetically manipulated to lack the predominant intestinal heparin sulfate protein, called syndecan-1, or all intestinal heparin sulfate proteins did not maintain a normal intestinal barrier, as assessed by leakage of serum proteins into the intestinal lumen (Fig. 1B and 1C). Treating these mice with the inflammatory cytokines TNF- α and interferon- γ exacerbated the barrier defect, which was consistent with the suspected role for these cytokines in the pathogenesis of protein-losing enteropathy. Similar

results were shown when the syndecan-deficient mice were surgically treated so as to increase portal-vein pressures, another well-known risk factor for the development of protein-losing enteropathy in humans. Remarkably, in the cytokine model of the disease, infusions of heparin sulfate analogues rescued the intestinal barrier defect.

These results are highly satisfying in that we now know that heparin sulfate proteins are essential for intestinal-barrier function and presumably for epithelial-junction formation and maintenance. But how can this be? One possibility is that the heparin sulfate proteoglycan extracellular domains somehow help establish cell–cell or cell–matrix adhesions that are necessary for the formation of intercellular junctions.³ Such a role for the syndecans in cell–matrix adhesions is evident in other cell systems. This theory would also explain how the soluble heparin sulfate analogues might rescue barrier function. Alternatively, the heparin sulfate proteoglycans might be required for binding growth factors or cytokines that are essential for securing the intestinal epithelial phenotype, replete with intact intercellular junction formation.

There is, however, one glitch in this argument. When examined with electron microscopy, a breakdown in the intercellular junctions was not demonstrated in syndecan-1–deficient mice unless they were also treated with the inflammatory cytokines to induce symptoms of protein-losing enteropathy. As suggested by Bode et al., it is possible that in the absence of other inciting agents, the loss of heparin sulfate proteins might cause a defect in barrier function by a mechanism separate from junction formation or maintenance. If so, then heparin sulfate proteins would have to act by affecting transcellular pathways of protein transport. Such pathways exist, but they are usually specific for certain proteins, such as the immunoglobulins.⁴

The data described by Bode et al. are exciting for the clinician. They are fully consistent with previous clinical and laboratory observations, and they provide a unifying concept to describe the pathogenesis of protein-losing enteropathy. Perhaps most important, they suggest a plausible strategy for treatment, because the heparin analogues that rescue barrier function are disabled in their ability to inhibit the clotting factors, thus reducing the odds of potential toxic effects. Plenty of preclinical studies will be required to further define clinical efficacy and to prove safety, but the chance for success is clearly present and the effort worthy. Such an approach might also be considered for treatment of other intestinal diseases, such as the chronic inflammatory bowel diseases, which, like protein-losing enteropathy, are partly caused by defective barrier function.

References

1. Bode L, Salvestrini C, Park PW, et al. Heparan sulfate and syndecan-1 are essential in maintaining murine and human intestinal epithelial barrier function. *J Clin Invest*. 2008; 118:229–38. [PubMed: 18064305]
2. Ma, TY.; Anderson, JM. Tight junctions and the intestinal barrier. In: Johnson, LR., editor. *Physiology of the gastrointestinal tract*. 4. Vol. 2. Burlington, MA: Elsevier Academic Press; 2006. p. 1559-94.
3. Morgan MR, Humphries MJ, Bass MD. Synergistic control of cell adhesion by integrins and syndecans. *Nat Rev Mol Cell Biol*. 2007; 8:957–69. [PubMed: 17971838]
4. Johansen, F-E.; Yen, EH.; Dickinson, BL., et al. Biology of gut immunoglobulins. In: Johnson, LR., editor. *Physiology of the gastrointestinal tract*. 4. Vol. 2. Burlington, MA: Elsevier Academic Press; 2006. p. 1067-90.

Figure 1. Intestinal Integrity: An Inquisition

In Panel A, the normal mouse intestine makes an effective barrier against free diffusion of certain ions, nutrient solutes, proteins, bacteria, and toxins so as to effectively separate the intestinal lumen (outside) from the lamina propria (inside). In Panel B, as found by Bode et al., syndecan-1-deficient mice have decreased intestinal-barrier function as a result of either defective intercellular junctions and increased paracellular leaks (dashed red line) or increased transcellular protein transport (solid red line). In Panel C, syndecan-1-deficient mice that were treated with inflammatory cytokines (such as tumor necrosis factor α [TNF- α] and interferon- γ) or surgically treated to increase portal-vein pressure have massively defective intercellular junctions and large protein leaks (thick dashed red lines) consistent with protein-losing enteropathy. In Panel D, infusions of heparin sulfate analogues completely reverse the intestinal-barrier dysfunction seen in syndecan-1-deficient mice treated with inflammatory cytokines.