EDITORIAL FOCUS | Epithelial Biology and Secretion

KLF-5 extends its fingers to desmosomes: the next frontier for enteric epithelial research?

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In this current issue of the American Journal of Physiology-Gastrointestinal and Liver Physiology, Liu and colleagues (3) provide a novel perspective on the regulation of intestinal barrier function by KLF5 through DSG2. The authors first examined this interaction using two mouse models of intestine-specific Klf5 knockout: a constitutive knockout mouse model (Klf5-floxed: Villin-Cre) and a tamoxifen-inducible knockout mouse model (Klf5-floxed: Villin-CreER T2). By analysis of colonic transcript levels of genes associated with cell junctions, the investigators discovered significantly decreased levels of the desmosomal cadherin Dsg2. The correlation between levels of KLF5 and DSG2 was confirmed by immunohistochemistry staining that showed decreased staining of DSG2 in tissues which had concurrently diminished KLF5 staining. Using transmission electron microscopy, the authors further demonstrated stark morphological differences in the desmosome complexes of cells from Klf5-floxed: Villin-CreER T2. They further found that the cell monolayers exhibited increased permeability, as determined by decreased transepithelial electrical resistance and an increased level of FITC-dextran pass-through concentration. As exhibited in the in vivo models, the investigators found that protein levels of DSG2 were significantly decreased, further confirming the link between KLF5 and DSG2. Intriguingly, DSG2 overexpression in the KLF5 knockdown cell line partially rescued the impairments in barrier function.

Liu et al. (3) beautifully demonstrated a novel influence of KLF5 on the intestinal epithelium through its interaction with the desmosomal cadherin, DSG2. The investigators comprehensively evaluated their findings in two in vivo models and confirmed the mechanisms involved by using an in vitro KLF5 knockdown cell line. Importantly, they evaluated a wide array of cell junction components, including cadherins, claudins, and occludins, and only found highly significant differences in DSG2, suggesting a highly specific action for KLF5. The authors illustrated an important ability of DSG2 overexpression to partially reverse the epithelial permeability al-

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terations caused by KLF5 knockdown. Because this rescue was only partial, however, KLF5 may act on additional factors or through other pathways to modulate epithelial barrier and function. Nonetheless, these findings are demonstrative of a unique, novel pathway that may be harnessed to influence epithelial barrier function.

The findings in this article may be relevant to disease states where intestinal barrier permeability can be a precipitant of the underlying pathophysiology. Intestinal permeability has been reported as a sensitive prognostic indicator for relapse in patients with Crohn’s disease (2), and multiple studies have revealed that intestinal epithelial structure and permeability are dysfunctional in at least a subset of individuals with IBD (1, 9). It would thus be interesting to determine whether KLF5 KO mice develop intestinal inflammation and, if so, the respective roles of intestinal barrier function and the enteric microbiota. Furthermore, intestinal barrier permeability has been found to be increased in subsets of patients with other gastrointestinal conditions like irritable bowel syndrome (13, 15). There are currently no Food and Drug Administration-approved therapies that target the intestinal epithelial barrier. This study thus adds significantly to our arsenal of knowledge geared toward understanding the mechanisms underlying epithelial permeability and may pave the way toward novel interventions for disease states where epithelial permeability is a contributing factor.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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