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EDITORIAL

Swimming Through the Gut: Implications of Fluid Transport on the Microbiome

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A primary physiologic function of mucosal epithelial cells is electrolyte transport. In tissues lined by epithelia, such as the lung and intestine, electrolyte transport is accomplished by active ion transport coordinated through a series of membrane transporters [1]. In Cl^- secreting epithelium, for instance, the rate-limiting step is entry of Cl^- via the Na–K-2Cl^- cotransporters [2], a family of proteins that mediate electroneutral transport of Na^+, K^+ and Cl^- ions across cellular membranes [1]. Exit of Cl^- across the apical membrane is accomplished by stimulation-dependent transport through chloride channels, the most prevalent of which is the cystic fibrosis transmembrane regulator (CFTR). Mutations in CFTR are associated with the clinical disease cystic fibrosis (CF) through presumed dehydration of mucosal surfaces [3].

Innate immunity in the intestine includes a combination of chemical, mechanical and environmental barriers to the invasion of luminal microbes [4–6]. Water transport and mucosal hydration function are thought to be necessary components of a normally protective barrier based on indirect data gathered from pathologic changes accruing from decreased or increased hydration (e.g., cystic fibrosis or cholera and enterotoxigenic *Escherichia coli*) [7, 8] and from observations of microbial evasion of normal mucosal clearance mechanisms [8, 9]. From this perspective, surprisingly little is known about the direct influence of water transport on bacterial-epithelial interactions.

The study by Musch et al. in this issue [10] addresses this issue head-on. They proposed that activation of electrogenic Cl^- secretion in the intestinal mucosa alters mucus makeup and the composition of the intestinal microbiome. The authors reported that lubiprostone, an agent used clinically in the treatment of constipation [10], stimulates electrogenic Cl^- secretion, and presumably water transport, in the jejunum, ileum and throughout the colon. Somewhat surprisingly, lubiprostone decreased the thickness of the inner mucus layer of the colon and fundamentally shifted the composition of stool microbiome. These studies provide immediate confirmation of our own work, where we recently reported that active electrogenic Cl^- secretion (elicited by lubiprostone) functions as a primitive innate defense mechanism, substantially shifting the colonic microbiota with notable changes in both Firmicutes and Bacteroidetes phyla of resident colonic bacteria [11]. In particular, the work by Musch et al. [10] and our own studies [11] reveal, among others, the increased association of *Lactobacillus* spp. in stool samples of lubiprostone-treated mice, which likely reflect a more "protective" microbiome. Indeed, the beneficial influences of lactobacilli are exemplified by their common use as probiotic agents [12, 13]. *Lactobacillus* spp. possess anti-inflammatory properties in addition to other host beneficial influences including colonization resistance, increased availability of nutrients to the intestine, and improved digestion [13]. The anti-inflammatory activity of colonic lactobacilli is attributable to cell surface proteins interacting with the host immune response [14]. In IL-$10^{-/-}$ spontaneous colitis mouse models, abnormal colonization of lactobacilli was present that when normalized, reduced levels of mucosal adherent bacteria and attenuated the development of colitis [15]. Of interest for the present work, colons from IL-$10^{-/-}$ mice have significant defects in activated Cl^- secretion, linked to decreased expression of the CFTR [16]. It is possible, therefore, that water transport, and associated changes to the mucus gel layer,

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promotes the colonization of lactobacilli, promoting colonic homeostasis.

Of particular relevance to the work by Musch et al. [10] is the possibility that lubiprostone could benefit patients with intestinal manifestations of CF. Intestinal symptoms are a common and debilitating complication of CF resulting from thickened mucus, perpetuating inflammation [17]. While this topic is controversial [18], the present work and work by others [19] have reported that the Cl^- secretory activity of lubiprostone largely bypasses the CFTR and, thus, lubiprostone may provide an alternative mechanism for mucosal hydration in these patients. Likewise, there is currently intense interest in elucidating the composition of the microbial communities in CF. In mouse models, significant shifts in the intestinal microbiota correlate with the most common clinical CF-associated mutations [20]. Whether treatment of patients with lubiprostone could influence the microbiome and overall intestinal health of such patients is anxiously anticipated by many.

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