Intestinal dysbiosis in celiac disease: Decreased butyrate production may facilitate the onset of the disease

Jiezhong Chen[a,1] and Luis Vitetta[a,b,1]

The intestinal microbiota is critical in the ontology of early-life immunity. The intestinal microbiota stimulates immune development through microbial-associated molecular patterns which bind and activate pattern recognition receptors (1). Meanwhile there is codevelopment of numerous antiinflammatory mechanisms that prevent excessive immune responses. Intestinal dysbiosis has been associated with metabolic diseases that occur in adult life. In their elegant study, Leonard et al. (2) report that intestinal dysbiosis is associated with celiac disease (CD) in infants. The mechanism elucidated was linked to adverse shifts of many bacterial metabolites, with a propensity for increased proinflammation over decreased antiinflammatory factors. We posit that the dysregulated interaction between the genus *Bifidobacteria* and butyrate-producing bacteria *Faecalibacterium prausnitzii* and *Clostridium clostridioforme* is critical in the development of CD indicated by this study.

The intestinal microbiota is composed of trillions of bacteria cells. The interactions among the microbes are complex and important. It has been demonstrated that the cross-feeding that occurs between *Bifidobacteria* and butyrate-producing bacteria such as *F. prausnitzii*, *Anaerostipes*, *Eubacterium*, and *Roseburia* species enhances butyrate production (3, 4). The production of butyrate in the intestines of infants is sophisticatedly programmed. A study has reported that butyrate shows a marked increase in concentration from 3- to 6- to 12-mo-old infants (5). From 6- to 12-mo-old infants, there was a fourfold increase in butyrate levels, reaching levels comparable to the infant mothers. The butyrate levels were correlated with abundance of butyrate-producing bacteria, namely, *F. prausnitzii* and *Eubacterium rectale*. Increased butyrate-producing bacteria are critical for the transition from an infant to an adult-like intestinal microbiota. As such, *Bifidobacteria* and *Faecalibacteria* among others (3) are important coexisting participants in butyrate-associated programming of the developing infant immune system.

Leonard et al. (2) characterize the dysbiosis before CD onset in their longitudinal study and find that proinflammatory bacteria such as *Dialister invisus*, *Parabacteroides sp.*, and *Lachnospiraceae* were increased, while butyrate-producing bacteria *F. prausnitzii* and *C. clostridioforme* as well as the antiinflammatory *Streptococcus thermophilus* were decreased (2). This may indicate insufficient production of butyrate in these patients. A recent study also reported that decreased abundance of *Bifidobacteria* was a causal factor in inflammatory diseases in infants, including CD (6). Deficits in *Bifidobacteria* resulted in increased populations of neutrophils, basophils, plasmablasts, and memory $CD8^+$ T cells, and increased blood levels of TNF-α, IL-6, and IL-17 with reduced antigen experienced regulatory T cells and nonclassical monocytes. The mechanism was associated with decreased levels of human mild oligosaccharides (HMO) utilization genes, indicating decreased production of HMO metabolites. These abutyrogenic effects could lead to decreased production of butyrate, disrupting the intestinal inflammatory tone. Butyrate stimulates antiinflammatory immune cells such as regulatory T cells and increases production of antiinflammatory cytokines (7, 8). Butyrate also decreases intestinal barrier permeability with increased mucus production to decrease inflammation caused by endotoxin and bacterial translocation (9). It is plausible that low butyrate production before the onset of CD may predicate an inflammatory tone skewed toward low antiinflammatory mechanisms, facilitating the initiation of CD.

[a]Research Department, Medlab Clinical, Sydney, NSW 2015, Australia; and [b]Faculty of Medicine and Health, The University of Sydney, Sydney, NSW 2006, Australia

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[1]To whom correspondence may be addressed. Email: jiezhong_chen@medlab.co or luis_vitetta@medlab.co.

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1 Y. Belkaid, T. W. Hand, Role of the microbiota in immunity and inflammation. *Cell* **157**, 121–141 (2014).
2 M. M. Leonard *et al.*; CD-GEMM Team, Microbiome signatures of progression toward celiac disease onset in at-risk children in a longitudinal prospective cohort study. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2020322118 (2021).
3 L. W. Chia *et al.*, *Bacteroides thetaiotaomicron* fosters the growth of butyrate-producing *Anaerostipes caccae* in the presence of lactose and total human milk carbohydrates. *Microorganisms* **8**, 1513 (2020).
4 D. Rios-Covian, M. Gueimonde, S. H. Duncan, H. J. Flint, C. G. de los Reyes-Gavilan, Enhanced butyrate formation by cross-feeding between *Faecalibacterium prausnitzii* and *Bifidobacterium adolescentis*. *FEMS Microbiol. Lett.* **362**, fnv176 (2015).
5 M. Nilsen *et al.*, Butyrate levels in the transition from an infant- to an adult-like gut microbiota correlate with bacterial networks associated with *Eubacterium rectale* and *Ruminococcus gnavus*. *Genes (Basel)* **11**, 1245 (2020).
6 B. M. Henrick *et al.*, Bifidobacteria-mediated immune system imprinting early in life. *Cell* **184**, 3884–3898.e11 (2021).
7 N. Arpaia *et al.*, Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* **504**, 451–455 (2013).
8 Y. Furusawa *et al.*, Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **504**, 446–450 (2013).
9 L. Peng, Z. R. Li, R. S. Green, I. R. Holzman, J. Lin, Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *J. Nutr.* **139**, 1619–1625 (2009).

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