Mirroring Amino Acids Hold Sway to Scare Pathobionts Away

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EDITORIAL

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All amino acids (aa), except glycine, are stereoisomers found in 2 different configurations in living organisms: the L-configuration and its chiral counterparts, the D-configuration. In mammals, L-aa are used to synthesize proteins, while microorganisms mostly use D-aa to synthesize their cell wall via a racemase enzyme converting L-aa into D-aa.[1] Accordingly, one might expect that D-aa supplementation will fuel intestinal bacteria overgrowth. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Umeda et al[2] unexpectedly reveal the beneficial role played by D-aa in tempering intestinal inflammation through microbiota modulation.

In inflammatory bowel diseases (IBDs), accumulating evidence highlights that the associated intestinal dysbiosis is characterized frequently by an increase in *Escherichia coli* pathobiont bacteria, together with a decrease in *Firmicutes* members, which could drive or foster chronic intestinal inflammation.[3] Moreover, various dietary factors are suspected to play a critical role in IBD pathogenesis through their impact on the intestinal microbiota.[4] Here, Umeda et al[2] first observed a decreased D-aa/L-aa ratio in fecal samples collected from UC patients compared with healthy individuals. The negative correlation between fecal D-aa abundance and microbial families such as *Enterobacteriaceae* further suggested that depletion of fecal D-aa could play a role in UC patients' dysbiosis. Strikingly, oral administration of 5 major D-aa (Ala, Ser, Glu, Trp, and Asn), either in their L or D configuration, revealed that D-aa supplementation could efficiently alleviate inflammation in mouse models of dextran sulfate sodium–induced colitis and of primary sclerosing cholangitis. Moreover, fecal microbiota transplantation from D-aa–treated mice into germ-free mice was sufficient to confer protection against dextran sulfate sodium–induced colitis, suggesting that the protective effect provided by D-aa supplementation is mediated, at least in part, by modulation of the intestinal microbiota. Various D-aa next were tested independently for their protective potential against colitis, identifying D-Ala, D-Trp, and D-Glu as central actors in microbiota composition modulation, especially by decreasing Proteobacteria relative abundance, and prevention of chronic intestinal inflammation.

Umeda et al[2] next focused their study on *Klebsiella pneumoniae*, *E coli*, and *Proteus mirabilis*, 3 Proteobacteria selectively decreased in mice treated with D-aa. They reported that D-aa supplementation could prevent colonic mucosal invasion by bacteria in the mouse model of cholangitis, as well as limit pore formation induced by *K pneumoniae* in murine organoid cultures. Bacterial growth experiments indicated that D-Ala supplementation inhibited the growth of the various Proteobacteria tested. Finally, Umeda et al[2] identified the bacterial *FtsZ* gene, essential for the last step of cell division, as strongly down-regulated in *E coli* and *K pneumoniae* upon D-ala supplementation. Overall, this study by Umeda et al[2] provides compelling evidence that select D-aa hold a potential therapeutic avenue, notably in IBD patients carrying an excess of Proteobacteria.

This work leaves open several questions. Although the microbiota was sufficient to transfer the protective effect conferred by D-aa supplementation, it cannot be excluded that D-aa also directly impacted the host, notably by modulating gene expression. The effect of D-aa supplementation on microbiota composition might indirectly restore butyrate-producing microbiota members, which frequently are reduced in IBD patients. Because butyrate is a potent inhibitor of histone deacetylases in intestinal epithelial cells,[5] it can be envisioned that intestinal D-aa impacts the epigenetic landscape in host epithelial and/or immune cells, and thereby modulates expression of antimicrobial peptides and genes involved in intestinal barrier function. Another point warranting further investigation relates to the depletion of fecal D-aa observed in IBD patients, which might be a cause, but also a consequence, of chronic intestinal inflammation. Similarly, the cause–consequence relationship between the fecal D-aa load and the relative abundance of various microbiota members remains to be elucidated.

The authors nicely reported how D-aa can inhibit *E coli* expansion in vitro and in vivo in mice, but further studies appear needed to confirm these observations in human beings. Among pathobionts, adherent-invasive *E coli* (AIEC) bacteria are thought to play an important role in the etiology of IBD.[6] AIECs are found encroached within the ileal mucosa of Crohn's disease (CD) patients, where they hold the potential to induce a chronic inflammatory response.[7] To date, no specific therapeutic approach targeting AIEC bacteria in CD patients have been developed, but clinical trials are ongoing to assess the efficiency of AIEC eradication in CD patients through antibiotics, phages therapy, or FimH blockage. The important role suggested here for D-aa in regulating the colibiome opens another innovative therapeutic approach to specifically inhibit AIEC intestinal colonization. Hence, these data are of great interest for future targeted modulation of the intestinal microbiota in IBD or individuals at risk of developing IBD.

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