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LETTER TO THE EDITOR

Simvastatin Therapy in Multiple Sclerosis Patients with Respect to Gut Microbiome-Friend or Foe?

Mehdi Toghi[1] · Sara Bitarafan[1]

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To the Editor;

There are some reports indicating positive effect of simvastatin in promoting remyelination in multiple sclerosis (MS) patients (Kremer et al. 2018). In addition to this effect, simvastatin also reported to have beneficial effects in the treatment of secondary progressive multiple sclerosis (SPMS) (Chan et al. 2017). Despite these positive effects of simvastatin in MS pathogenesis, its effect on gut microbiome of patients has been ignored in the literature.

Prescribed pharmaceuticals along with other factors such as the host genetics, diet, lifestyle, mode of delivery and antibiotic exposure could affect gut microbiome. When these factors render the gut microbiome out of balance, there may be an induced imbalance between pro- and anti-inflammatory responses that could lead to disease. This proposed disease model is known as gut microbiome dysbiosis that results in, or are a result of, disease states. Further, gut dysbiosis has been associated with intestinal barrier disruptions. Reduced integrity of tight junction protein complexes could increase intestinal permeability, and therefore bacterial antigens can pass out of the intestinal lumen and move to different parts of the body. As a result, increased levels of antigens in the blood circulation could have systemic inflammatory effects. Systemic translocation of bacterial antigens can have a profound effect on CNS immunity and impact the integrity of the blood–brain barrier, which facilitates the ultimate passage of autoreactive lymphocytes into the CNS. Importantly, there is some evidence that gut microbiome dysbiosis has a prominent role in MS pathogenesis (Kirby and Ochoa-Repáraz 2018) (Fig. 1).

Statins, as a pharmaceutical product, possess direct antibacterial activity, and simvastatin exerts the greatest antibacterial activity against gram-positive bacteria in comparison with other statins (Ko et al. 2017). This is important because gram-positive *Firmicutes* that constitute the most predominant phyla in the healthy human gut are the most prominent producers of human colonic short-chain fatty acids (SCFAs), especially butyrate (Ohira et al. 2017). Notably, long-chain fatty acids (LCFAs) worsen experimental autoimmune encephalomyelitis (EAE) via promoting $CD4^+$ T cell differentiation toward TH1 and TH17, and decreasing Treg differentiation; however, SCFAs ameliorate EAE via promoting Treg differentiation. In parallel, most of the *Firmicutes* phylum members were commonly reported to be reduced in MS guts (Mowry and Glenn 2018).

Faecalibacterium prausnitzii is an important commensal bacterium of the *Firmicutes* phylum that has been shown to exert local and systemic anti-inflammatory effects by reducing the pro-inflammatory cytokine IL-17, increasing IL-10, and synthesizing microbial anti-inflammatory molecule (MAM), an inhibitor of NF-κB and the short chain fatty acid, butyrate. This bacterium is very sensitive to its environment and presence of acute or moderate inflammation negatively affect its proportion. The relative abundance of *F. prausnitziiis* in the gut is considered as a 'sensor and a marker of health', and there is some evidence that this bacterium is reduced in MS patients (Francis and Constantinescu 2018).

In parallel, a recent study undertaken by Caparrós-Martín has demonstrated that statin therapy in mice results in a significant reduction in the abundance of many gram-positive operational taxonomic units (OTUs) within the phylum *Firmicutes*. Importantly, reduced level of *Firmicutes* in the

✉ Mehdi Toghi
toghi67@gmail.com

[1] Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran

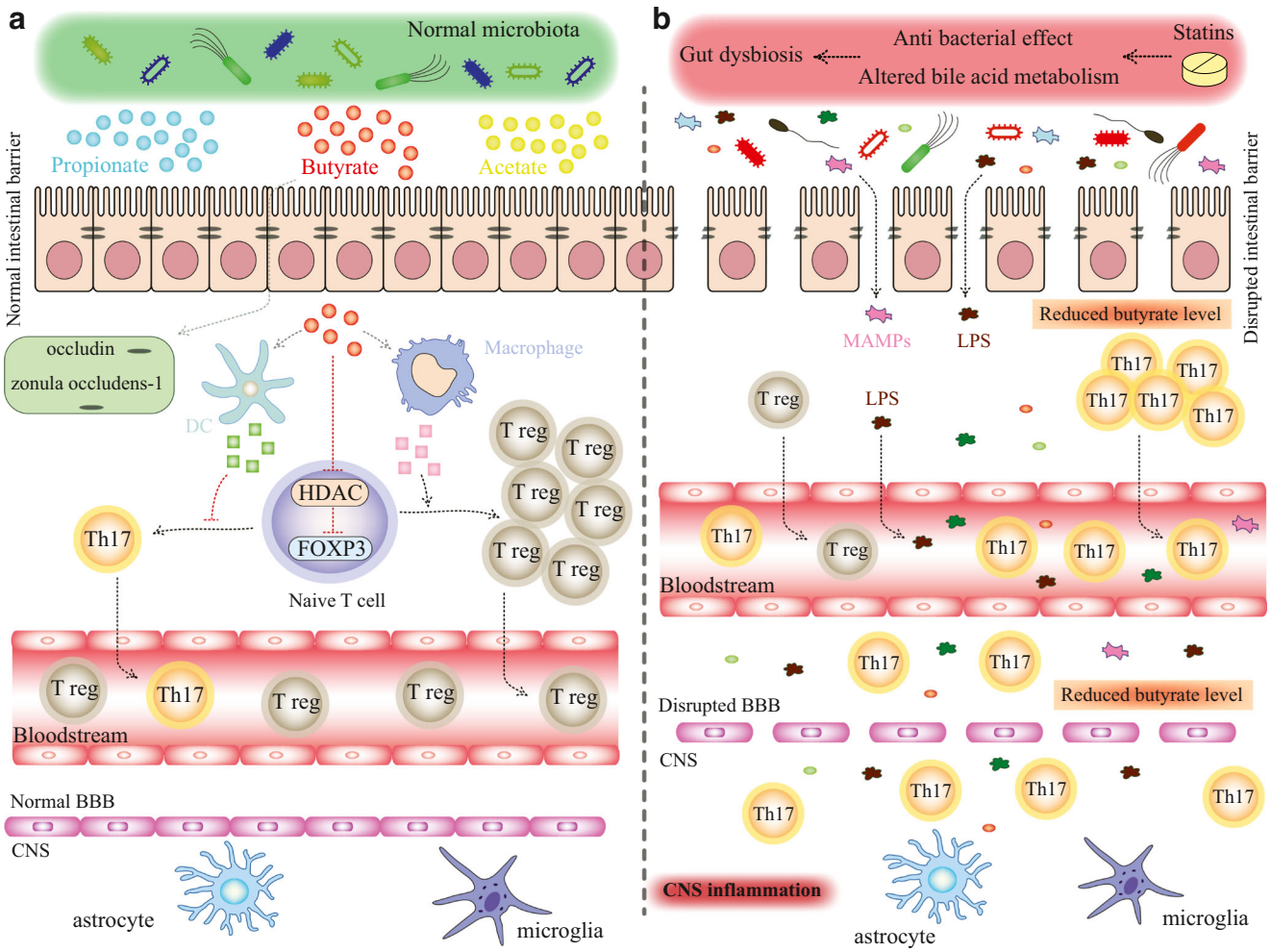

Fig. 1 **a** Commensal gut bacteria ferment dietary fiber into short chain fatty acids (SCFAs) like butyrate. Butyrate promote differentiation of naïve T cells into regulatory T cells and suppress production of Th17 cells. Butyrate also activates expression of tight junction proteins and therefore reduces intestinal permeability. **b** Gut dysbiosis resulted from long term use of medications, reduces SCFAs levels. Reduction in SCFAs then leads to increased intestinal permeability, creation of pro-inflammatory milieu and also reduced integrity of BBB

intestinal microbiota after statin treatment may lead to a dramatic reduction in butyrate production. The authors, on the other hand, reported enlarged bile acid (BA) pool in the gut of the statins-treated mice. Accordingly, Cyp27a1 mRNA was up-regulated in the liver of the statin-treated mice, which explains the altered BA profile observed in the gut. Therefore, the deregulation of BA metabolism after statin therapy would contribute to the progressive selection of BA-tolerant microorganisms in the gut, which then leads to gut microbiome dysbiosis (Caparrós-Martín et al. 2017).

Combined, although simvastatin (and perhaps other statins) has a beneficial role in promoting remyelination (and also treatment of SPMS patients in a dose-dependent manner), they may induce/exacerbate gut microbiome dysbiosis, and high doses should be used cautiously in the long-term treatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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