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**Diet is among the most important factors contributing to intestinal homeostasis, and basic functions performed by the small intestine need to be tightly preserved to maintain health. Little is known about the direct impact of high-fat (HF) diet on small-intestinal mucosal defenses and spatial distribution of the microbiota during the early phase of its administration. We observed that only 30 d after HF diet initiation, the intervillous zone of the ileum—which is usually described as free of bacteria—became occupied by a dense microbiota. In addition to affecting its spatial distribution, HF diet also drastically affected microbiota composition with a profile characterized by the expansion of Firmicutes (appearance of *Erysipelotrichi*), Proteobacteria (*Desulfovibrionales*) and Verrucomicrobia, and decrease of Bacteroidetes (family S24-7) and *Candidatus arthromitus*. A decrease in antimicrobial peptide expression was predominantly observed in the ileum where bacterial density appeared highest. In addition, HF diet increased intestinal permeability and decreased cystic fibrosis transmembrane conductance regulator (*Cftr*) and the Na-K-2Cl cotransporter 1 (Nkcc1) gene and protein expressions, leading to a decrease in ileal secretion of chloride, likely responsible for massive alteration in mucus phenotype. This complex phenotype triggered by HF diet at the interface between the microbiota and the mucosal surface was reversed when the diet was switched back to standard composition or when mice were treated for 1 wk with rosiglitazone, a specific agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ). Moreover, weaker expression of antimicrobial peptide-encoding genes and intervillous bacterial colonization were observed in *Ppar-γ*–deficient mice, highlighting the major role of lipids in modulation of mucosal immune defenses.**

high-fat diet | microbiota | antimicrobial peptides | PPAR-γ | CFTR

Humans coexist with a large number of microorganisms called microbiota. The intestine is populated by more than 100 trillion microbial cells, and the rules of this coexistence need deciphering. These numbers are essentially accounted for by the colon (1). In the small intestine (SI), a gradient of microbial density and community exists from the duodenum, which is relatively poorly populated, to the distal ileum/cecum, which tends to resemble the colon (2, 3). This holobiont has been established by the strong mutual selective pressure of coevolution and its homeostasis is essential to health (4, 5). Changes in diet composition are among the most influential conditions altering this balance, possibly with pathological consequences whose mechanisms can be experimentally addressed in the mouse, which has developed a similar condition of mutualistic symbiosis.

Intestinal epithelial cells (IECs) are on the front line of this confrontation. The SI epithelium is extensively folded into crypts and villi, which increase the surface available for food digestion and nutrient absorption (6). IECs develop an array of strategies to keep these complex and dynamic microbial communities at bay. IECs act as sentinels by expressing a wide range of efficient pattern recognition receptors that control innate defense mechanisms regulating the proximity and composition of the microbiota (7, 8). Other elements of epithelial barrier capacity comprise tight junctions (9, 10) and production/secretion of antimicrobial peptides (AMP) (11, 12). The antibacterial lectin Reg3γ promotes the spatial segregation of microbiota and host in the intestine (13), the secretion and organization of the mucus layer that provides physico-chemical protection and a matrix for secreted antimicrobial molecules (14, 15), and the control of electrolyte balance (16, 17) contribute to this defense. The microbiota itself participates in strengthening mucosal defenses by stimulating epithelial renewal (18–20), production of AMP (21), cytoprotection against xenobiotics (22, 23), immune maturation, increase of intestinal impermeability (24), and modulation of mucus quality and penetrability (25). Hence, the direct engagement of the intestinal epithelium by the microbiota remains rare and limited because most of the commensal bacteria

## Significance

Our study aimed at exploring the intersection of high-fat diet, mucosal immune defenses, and microbiota. It remains unclear how diet imbalance toward excessive fat intake leads to secondary pathological effects on host physiology through the microbiota. We show that a short period of consumption of high-fat diet alters the small-intestinal defenses and that the biochemistry of the ileum is drastically modified, leading to physiological changes close to that observed in cystic fibrosis. We identified peroxisome proliferator-activated receptor-γ as major regulator of mucosal defenses upon exposure to fat excess. As a result, our work provides a fundamental understanding of the underlying cause of severe chronic disorders associated with Western diet.

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Data deposition: The 16S rRNA gene sequence data have been deposited into the NCBI Sequence Read Archive database, www.ncbi.nlm.nih.gov/sra (BioProject accession nos. PRJNA306818 and PRJNA340242).

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