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REVIEW

Changes in the Luminal Environment of the Colonic Epithelial Cells and Physiopathological Consequences

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Evidence, mostly from experimental models, has accumulated, indicating that modifications of bacterial metabolite concentrations in the large intestine luminal content, notably after changes in the dietary composition, may have important beneficial or deleterious consequences for the colonic epithelial cell metabolism and physiology in terms of mitochondrial energy metabolism, reactive oxygen species production, gene expression, DNA integrity, proliferation, and viability. Recent data suggest that for some bacterial metabolites, like hydrogen sulfide and butyrate, the extent of their oxidation in colonocytes affects their capacity to modulate gene expression in these cells. Modifications of the luminal bacterial metabolite concentrations may, in addition, affect the colonic pH and osmolarity, which are known to affect colonocyte biology per se. Although the colonic epithelium appears able to face, up to some extent, changes in its luminal environment, notably by developing a metabolic adaptive response, some of these modifications may likely affect the homeostatic process of colonic epithelium renewal and the epithelial barrier function. The contribution of major changes in the colonocyte luminal environment in pathological processes, like mucosal inflammation, preneoplasia, and neoplasia, although suggested by several studies, remains to be precisely evaluated, particularly in a long-term perspective. *(Am J Pathol 2017, ■: 1–11; http://dx.doi.org/10.1016/j.ajpath.2016.11.015)*

Q6 The colonic epithelium is a dynamic structure with a rate of renewal among the fastest in the body. This renewal is made possible through a lifelong and highly coordinated sequence of events starting with mitosis of pluripotent stem cells[1] and ending with anoikis of fully mature cells in the colonic lumen.[2] The colonic epithelium, which is organized in crypts separated by a flat surface, is notably responsible for the physiological function of water and electrolyte absorption from the lumen to the bloodstream. This corresponds to the polarized structure of absorptive colonocytes, which are facing the luminal content. This latter is a complex and not fully characterized mixture of water, bacteria, undigested or partially digested dietary/endogenous compounds, and bacterial metabolites. The colonic epithelium can be viewed as a selective barrier in close proximity with this intestinal luminal content.[3] Occasionally, the homeostatic processes of colonic epithelial self-renewing and/or epithelium normal functions are disrupted; and such alterations may be associated with different colonic physiopathological states, including diarrhea,[4] mucosal inflammation, and preneoplasic/neoplasic lesions.[5] The objectives of this article are as follows: i) to illustrate by some typical examples the impact of the macronutrient composition of the diet on the characteristics of the large intestine luminal contents, ii) to give an overview on the effects of changes of the luminal environment on colonic epithelial cell physiology and metabolism, with a focus on the effects of bacterial metabolites, and iii) to examine to what extent such

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changes, above the adaptive capacity of colonocytes, may have significant consequences for the gut health.

Regarding the recognition of microbial ligands by intestinal epithelial cells, and the effects of bacterial toxins (eg, colibactin, *Bacteroides fragilis* toxin, and fragilysin) on colonic epithelial cells, the readers are invited to refer to recent reviews[3,6] because these important aspects will not be presented herein.

Effects of the Diet on the Luminal Environment of the Large Intestine

In the colon, bacteria metabolize undigested or partially digested substrates available from endogenous (digestive secretions, exfoliated cells, and mucins) and dietary sources.[7] Human dietary intervention studies revealed that the macronutrient composition of the diet can affect the amount of metabolites produced by the microbiota in the large intestine. In fact, dietary undigestible polysaccharides increase the fecal concentration of short-chain fatty acids,[8] whereas high-fat diets increase bile acid secretion in the small intestine that leads to high fecal concentrations of microbiota-derived secondary bile acids, such as deoxycholic acid.[9] High-protein diets increase fecal concentrations of amino acid–derived bacterial metabolites, such as branched-chain fatty acids, phenolic compounds, hydrogen sulfide, and ammonia.[10] Q7

Colonic luminal pH may also be modified by dietary changes. However, this latter parameter is not easily accessible in humans, and most values are recovered from measurement of pH in animal models. For instance, a high-protein diet increases the pH in the rat colon content after 2 days in association with increased ammonia concentration.[11] In humans, most of the data referred to the effects of dietary changes on fecal pH, which reflects the pH in the distal part of the large intestine (ie, rectum). Ingestion of nondigestible carbohydrates decreases the fecal pH in adults,[12] whereas a high-protein and low carbohydrate diet increases this parameter.[13]

Collectively, these studies provide strong evidence that the human rectal environment (thus inferred from feces analyses) is dependent on the macronutrient composition of the diet.

Briefly, regarding the composition of the colonic microbiota, this complex parameter, although considered as globally stable at the individual level,[14] can be rapidly affected by environmental modifications, notably from dietary origin.[15] Concerning luminal substrate availability, there is evidence that this parameter plays a major role in determining the rate of production of bacterial metabolites.[6,16,17]

Modified luminal bacterial metabolite composition in inflammatory bowel diseases has been reported.[18] However, it is often difficult to determine whether such modifications are causes and/or consequences of these diseases. In the same line of thinking, although intestinal microbiota dysbiosis has been reported in colorectal cancers,[19] and role of selected bacteria has been anticipated,[20] it remains a hard task to determine what are the respective causal links between the bacterial composition/bacterial metabolic capacity/bacterial metabolite composition and the related pathophysiological situations.

In this overall complicated context, we review herein the effects of individual changes in the luminal environment (bacterial metabolite composition, pH, and osmolarity) on colonic epithelial cells and their potential implications in several digestive diseases.

Bacterial Metabolites and Colonic Epithelium Energy Metabolism

The gastrointestinal tract consumes as much as 20% of the whole body oxygen consumption, although it represents approximately 5% of total body weight.[21] Postprandial hyperemia is concomitant with enhanced intestinal oxygen uptake from the arterial blood, presumably to fuel the digestive and absorptive processes.[22] In contrast with the arterial partial pressure of oxygen, this latter parameter in the cecal luminal content is extremely low, not exceeding 1 mmHg.[23] However, oxygen from the host intestinal tissue can diffuse into the lumen, resulting in a radial gradient of oxygen-tolerant bacteria from the tissue to the lumen.

In the gastrointestinal tract, the intestinal epithelial cells are characterized by high energy demand, notably because of the rapid renewal of the epithelium and associated anabolic metabolism, and the activity of Na/K ATPase that allows sodium extrusion at the basolateral membranes.[21]

Modification of the partial pressure of oxygen inside colonocytes may affect their metabolism and physiology.[24] In active inflammatory bowel diseases, a metabolic shift toward hypoxia is observed, serving as an endogenous alarm signal in colonocytes.[25] Interestingly, when colon epithelial cells are challenged by hypoxia, up-regulation of the proto-oncogenes *c-fos* and *c-jun* is observed,[26] reinforcing the view that hypoxia acts in colonocytes on genes related to important physiopathological functions.[27]

Absorptive colonic epithelial cells use fuel substrates from both luminal and blood origin. Fuels from arterial origin are mainly L-glutamine, L-glutamate, L-aspartate, and D-glucose. Short-chain fatty acids (namely, acetate, propionate, and butyrate) are major luminal fuels for colonocytes. They are produced by the microbiota from undigestible carbohydrates[28] and several amino acids originating from undigested proteins.[29] Among short-chain fatty acids, butyrate is characterized by its capacity to inhibit endogenous substrate oxidation.[30] Data showing that butyrate uptake is impaired in inflamed colonic mucosa suggest that the reduction of butyrate availability may decrease the physiological functions of this short-chain fatty acid in colonocytes.[31] As a matter of fact, in addition to act as a luminal fuel in colonocytes, butyrate acts as a regulator of gene expression in colonocytes[32] (Figure 1). Mitochondrial [F1] metabolism of butyrate in colonocytes is likely a way to

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