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Colon epithelial cell turnover depends on microbiota-derived lactate

Toshihiko Okada[1, 2], Shinji Fukuda[3, 6], Koji Hase[4, 6], Shin Nishiumi[7], Yoshihiro Izumi[7], Masaru Yoshida[7, 8], Teruki Hagiwara[1], Rei Kawashima[1], Motomi Yamazaki[1], Tomoyuki Oshio[1], Takeshi Otsubo[1], Kyoko Inagaki-Ohara[1], Kazuki Kakimoto[1, 2], Kazuhide Higuchi[2], Yuki I. Kawamura[1], Hiroshi Ohno[3, 6], ○Taeko Dohi[1, 5] *

[1]Dept Gastroenterology, Research Center for Hepatitis and Immunology, Research Institute, National Center for Global Health and Medicine,
[2]2nd Dept of Internal Medicine, Osaka Medical College,
[3]Laboratory for Epithelial Immunobiology,
[4]Bioenvironmental Epigenetics, RIKEN Research Center for Allergy and Immunology,
[5]Open Laboratory for Allergy Research, RIKEN Research Center for Allergy and Immunology,
[6]Graduate School of Nanobioscience, Yokohama City University,
[7]Div of Gastroenterology, Dept of Internal Medicine, Kobe University Graduate School of Medicine,
[8]Div of Metabolomics Research, Dept of Internal Medicine, Kobe University Graduate School of Medicine

The gastrointestinal (GI) tract must adapt to drastic changes in the lumenal environment to maintain homeostasis, and responses to ingested food are the most fundamental physiological adaptations. Epithelial cells (EC) in the GI tract undergo rapid self-renewal, with a new gut lining produced approximately every 3 days. However, the turnover rate is not always constant. For example, gut EC proliferation rates undergo circadian fluctuation in rodents and humans, which alters the morphology and function of the GI tract. In normal human rectal biopsies, H-thymidine incorporation into cells is higher at night and lower in the afternoon. Oral food intake most influences this turnover as well as morphology and function of intestinal epithelial cells. However, how exactly these processes are regulated, particularly in the large intestine, remains unclear. In this study, we identified microbiota-derived lactate as a major factor to induce enterocyte hyperproliferation in starvation-refed mice. Colonic epithelial cell turnover, enumerated as BudU incorporated cells/crypt, arrested during a 12- to 36-h period of starvation and thereafter, proliferation exceeded control levels by approximately 3-fold at 12 h. This transient excessive cell proliferation continued for 24 h and returned to basal levels by 76 h after refeeding, and was observed in several mouse strains, irrespective of gender or age. Because a 12-h starvation period would be expected to occur on a daily basis, we also examined the daily changes in colonic EC proliferation without a controlled starvation period. As expected, considerable fluctuation in the number of BrdU+ cells was observed. Enhanced epithelial cell proliferation depends on the increase in live *Lactobacillus murinus*, lactate production and dietary fiber content, as determined by 16s rRNA sequence of flora, metabolome analysis of the intestinal contents, and the experiments using germ free or knotobiotic mice. The comparison of gnotobiotic mice monoassociated with lactate-producing *Bifidobacterim longum* subsp. *infantis* (*B. infantis*) and non-lactate-producing *Bacteroides thetaiotaomicron* (*B. thetaiotaomicron*) demonstrated that lactate producing *B. infantis* but not *B. thetaiotaomicron* induced hyperproliferation of the colon epithelia, indicating that the bacteria metabolite lactates rather than bacterial components plays a major role to induce accelerated cell turnover. In the model of colon tumorigenesis induced by injection of azoxymethane, mice exposed to a carcinogen during refeeding develop more aberrant crypt foci than mice fed ad libitum. Carcinogen exposure followed by fasting-refeeding greatly reduced the incidence of aberrant crypt foci. Our results indicated that the content of food, microbiota, as well as eating behavior directly influenced the incidence of colon tumorigenesis.