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Gut microbiota modulate CD8$^+$ T cell immunity in gastric cancer through Butyrate/GPR109A/HOPX

Xiang Yu [1], Jinzhou Ou [1], Lingzhi Wang [1], Zhenyuan Li [1], Yingxin Ren [1], Lang Xie [2], Zhian Chen [1], Junxian Liang [2], Guodong Shen [1], Zhaowei Zou [2], Cuiyin Zhao [1], Guoxin Li [1], Yanfeng Hu [1]

Affiliations

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Abstract

The gut microbiota and Short-chain fatty acids (SCFAs) can influence the progression of diseases, yet the role of these factors on gastric cancer (GC) remains uncertain. In this work, the analysis of the gut microbiota composition and SCFA content in the blood and feces of both healthy individuals and GC patients indicated that significant reductions in the abundance of intestinal bacteria involved in SCFA production were observed in GC patients compared with the controls. ABX mice transplanted with fecal microbiota from GC patients developed more tumors during the induction of GC and had lower levels of butyric acid. Supplementation of butyrate during the induction of gastric cancer along with H. pylori and N-methyl-N-nitrosourea (MNU) in WT in GPR109A$^{-/-}$mice resulted in fewer tumors and more IFN-γ$^+$ CD8$^+$ T cells, but this effect was significantly weakened after knockout of GPR109A. Furthermore, In vitro GC cells and co-cultured CD8$^+$ T cells or CAR-Claudin 18.2$^+$ CD8$^+$ T cells, as well as in vivo tumor-bearing studies, have indicated that butyrate enhanced the killing function of CD8$^+$ T cells or CAR-Claudin 18.2$^+$ CD8$^+$ T cells against GC cells through G protein-coupled receptor 109A (GPR109A) and homologous domain protein homologous box (HOPX). Together, these data highlighted that the restoration of gut microbial butyrate enhanced CD8$^+$ T cell cytotoxicity via GPR109A/HOPX, thus inhibiting GC carcinogenesis, which suggests a novel theoretical foundation for GC management against GC.

Keywords: CD8+ T cell immunity; Gut microbiota; butyrate; gastric cancer.

Figures

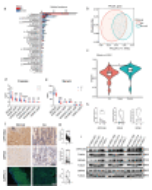

Figure 1. (a) Differential analysis of microbial...

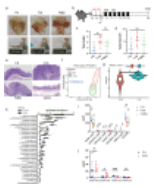

Figure 2. ABX mouse transplantation of GC...

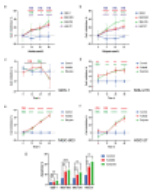

Figure 3. (a-b) Proliferation in control GES-1...

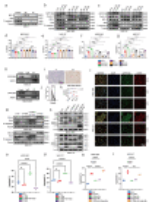

Figure 4. (a) Differences in protein expression...

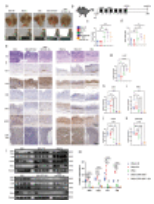

Figure 5. At week 12 following the...

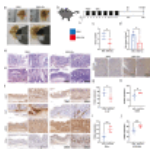

Figure 6. Mice with *H. pylori* SS1+MNU-induced...

All figures (10)

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