Medicine, Drug discovery

Pathogenic metabolites in *Helicobacter pylori* that exacerbate gastritis

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Abstract

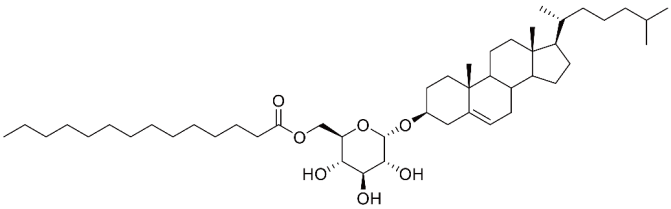
In this study, we clarified the mechanism by which *Helicobacter pylori (H. pylori)*, a gram-negative bacterium, causes gastritis. *H. pylori* induces gastritis by extracting cholesterol from host cells and subsequently adds sugars and lipids within the bacterium to produce compounds that induce gastritis. These compounds are recognized by the host receptors-Mincle and DCAR, leading to the development of gastritis. Inhibition of this modification pathway prevents *H. pylori*-induced gastritis.

Background & Results

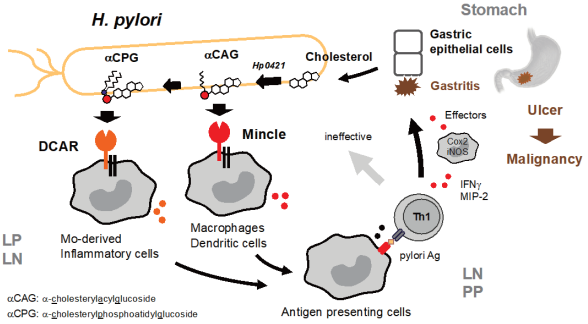
H. pylori is believed to cause chronic gastritis and gastric cancer. It is estimated that *H. pylori* infects approximately 50% of the world's population, including nearly 60 million people in Japan. Usually, it is possible to eradicate *H. pylori* by using antibacterial drugs and gastric acid secretion inhibitors; however, cases of unsuccessful treatment after two rounds of eradication and disruption of the bacterial flora balance by antimicrobial agents are challenge. *H. pylori* is believed to cause gastritis by over-activating the host immune system, but the surface of *H. pylori* has a structure that cannot be recognized by innate immune receptors on macrophages and dendritic cells; therefore, the mechanism by which it activates the host immune system remains unclear. The significance of this study proposes a novel therapeutic concept that allows *H. pylori* to "coexist" in the host body without using antimicrobial agents and yet suppress *H. pylori*-induced gastritis.

Significance of the research and Future perspectives

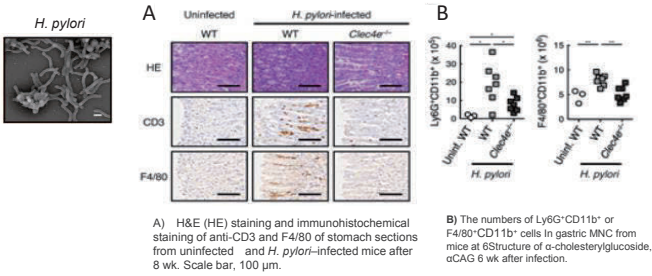
In this study, we identified a lipid component of *H. pylori* that induces the production of inflammatory cytokines in the host (mice). They found that the substance is recognized by a host innate immune receptor called Mincle. When mice lacking the gene for Mincle, the receptor for αCAG, were infected with *H. pylori*, there was no difference in the number of organisms in their bodies compared with wild-type mice infected with *H. pylori*. Despite this lack of difference in the number of bacteria in their bodies, the mice showed less activation of immune cells and less gastritis. Furthermore, we found that αCPG, which is structurally similar to αCAG, was recognized by an innate immune receptor called DCAR and activated the host immune system. Next, we created a strain of *H. pylori* lacking the gene for cholesteryl glucosyltransferase (Hp0421), which is required for the synthesis of αCAG and αCPG. Mice infected with this strain of *H. pylori* showed less gastritis than those infected with wild-type *H. pylori*, although the number of bacteria remained the same. Hp0421 is an enzyme unique to the genus *Helicobacter*, to which *H. pylori* belongs, making it a highly specific and safe therapeutic target. This treatment suppresses the inflammatory response caused by *H. pylori*, which is a very different concept from eradication, and suggests that "coexistence" rather than eradication may be a treatment option to prevent *H. pylori* from causing harm to the host.



Structure of α-cholesterylglucoside, αCAG



Main Figures



A) H&E (HE) staining and immunohistochemical staining of anti-CD3 and F4/80 of stomach sections from uninfected and *H. pylori*–infected mice after 8 wk. Scale bar, 100 μm.

B) The numbers of Ly6G+CD11b+ or F4/80+CD11b+ cells in gastric MNC from mice at 6Structure of α-cholesterylglucoside, αCAG 6 wk after infection.

Identification of host-side receptors that recognize αCAG

Patent	Japanese Patent Application No. 2020-157742
Treatise	Nagata, Masahiro; Toyonaga, Kenji; Ishikawa, Eri et al. Helicobacter pylori metabolites exacerbate gastritis through C-type lectin receptors, Journal of Experimental Medicine. 2021 Jan 4;218(1): e20200815. doi: 0.1084/jem.20200815.
URL	https://resou.osaka-u.ac.jp/ja/research/2020/20200929_4 http://www.biken.osaka-u.ac.jp/achievement/research/2020/146 https://medical.nikkeibp.co.jp/leaf/mem/pub/report/202012/568092.html?pr=1
Keyword	chronic gastritis, helicobacter pylori, C-type lectin receptors, cholesteryl glucosyltransferase