Press Release

Keio University

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Keio University School of Medicine
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Bile Acids Associated with Longevity: Novel bile acid biosynthetic pathways enriched in centenarian microbiome

A joint research team has discovered that stool samples from Japanese centenarians contain elevated levels of a bile acid called isoallo-lithocholic acid (isoalloLCA) and has identified intestinal bacterial species that can produce this bile acid. The team was led by Professor Kenya Honda of the Department of Microbiology and Immunology at Keio University School of Medicine, who also serves as Team Leader for the Laboratory for Gut Homeostasis at the RIKEN Center for Integrative Medical Sciences. The team also found that isoalloLCA was capable of exerting potent antimicrobial effects against gram-positive multidrug-resistant pathogens (See Fig. 1).

These findings provide a basis for developing a way to prevent and treat infectious diseases in humans and may help unlock the secret of healthy longevity.

The results of this research were published in the online edition of the international journal *Nature* on July 30, 2021 (Japan Standard Time).

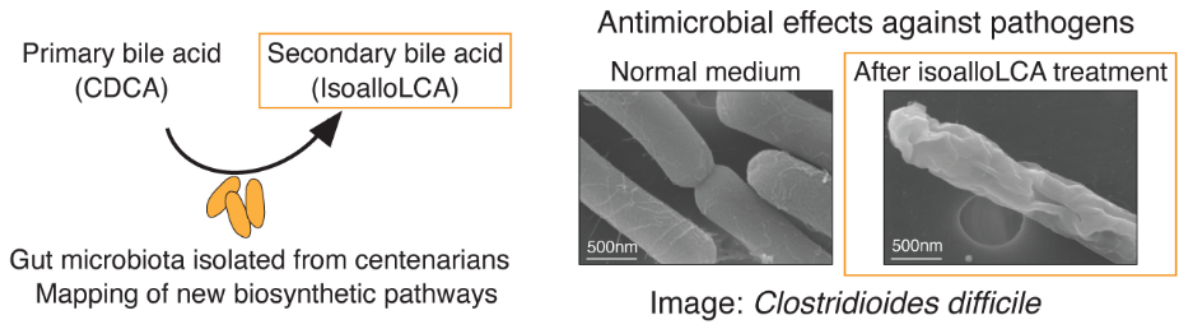

Fig. 1: Discovery and effects of the biosynthetic pathway that produces isoallo-lithocholic acid (isoalloLCA), a secondary bile acid unique to centenarians

1. Research Background

To probe the potential link between microbiota composition and longevity, the group collected stool samples from centenarians in Japan (average age 107) and analyzed their gut microbiota. Results showed that, compared to elderly individuals (aged 85–89 years old) and younger individuals (aged 21–55 years old), the intestinal tracts of centenarians had an increased number of various bacterial species (*Alistipes*, *Parabacteroides*, *Bacteroides*, *Clostridium*, *Methanobrevibacter*, etc.). Since bacterial genes involved in bile acid metabolism were more abundant in the stool samples of centenarians than the other groups, the research group analyzed fecal bile acid levels. The results demonstrated that centenarians have a significant increase in isoalloLCA, a secondary bile acid generated by intestinal bacteria. However, the intestinal bacteria and biosynthetic pathways for isoalloLCA production had not been described previously.

2. Research Significance and Future Development

Bile acid compounds were incubated with bacterial strains isolated from centenarians. The research group found that *Parabacteroides merdae*, *Odoribacter laneus*, and *Odoribacteraceae* strains effectively produced isoalloLCA.

Analysis of sequences of the genomes of bacterial isolates revealed that the isoalloLCA-producing bacterial strains mentioned above commonly possessed an enzyme with homology to 5α-reductase (5AR). In addition, the enzyme 3β-hydroxysteroid dehydrogenase (3βHSDH), which is thought to be involved in bile acid metabolism, was also found to be present adjacent to 5AR. The deletion of the 5AR or 3βHSDH gene in *Parabacteroides merdae* strain abrogated the production of isoalloLCA. IsoalloLCA was also found to be elevated *in vivo* by the colonization of germ-free mice with *Odoribacteraceae* strains.

Since bile acids have been reported to inhibit the growth of pathogenic bacteria, the group tested whether isoalloLCA had similar effects and found that it inhibited the growth of gram-positive pathogens at extremely low concentrations. *Clostridioides difficile*, a gram-positive pathogenic bacterium, is known to elicit problematic healthcare-associated infections. When mice infected with *C. difficile* were orally administered with an isoalloLCA-producing *Odoribacteraceae* strain, intestinal *C. difficile* levels were significantly suppressed.

These results suggest that isoalloLCA provided colonization resistance against gram-positive pathogens, thereby promoting the maintenance of a healthy intestinal environment. IsoalloLCA-producing gut microbiota isolated from centenarians may be clinically applicable in the prevention and treatment of intestinal gram-positive pathogen infections.

3. Notes

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1. Advanced Research & Development Programs for Medical Innovation (LEAP)
   Title of Research Development Project: *Development of therapeutic cocktails of bacteria isolated from the gut microbiota*
2. Grants-in-Aid for Scientific Research Program (KAKENHI)
   Name of Research Project: *Unraveling the principles of microbiota function for rationally-designed biotherapeutics*

This research was also carried out with the support of the Terumo Life Science Foundation.

4. Research Paper

Title: *Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians*

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