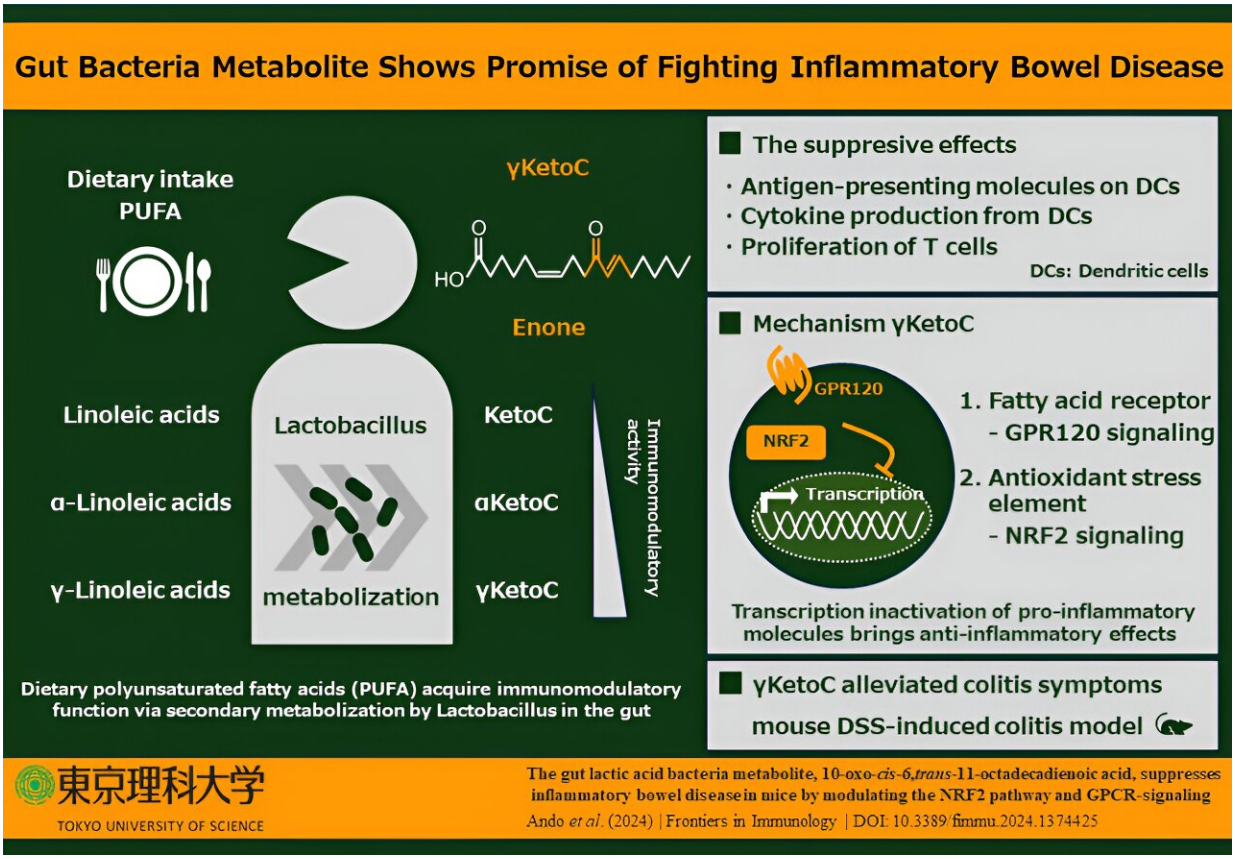
Gut bacteria metabolite shows promise in fighting inflammatory bowel disease

May 7 2024



Gut bacteria metabolite holds potential in combating inflammatory bowel disease. Credit: Chiharu Nishiyama from Tokyo University of Science, Japan

Gut microbiota or the population of microbial inhabitants in the intestine, plays a key role in digestion and maintenance of overall health.

Any disturbance in the gut microbiota can, therefore, have a systemic impact. Intestinal microbes metabolize dietary components into beneficial fatty acids (FAs), supporting metabolism and maintaining host body homeostasis.

Metabolites originating from polyunsaturated fatty acids (PUFAs), influenced by gut microbes such as Lactobacillus plantarum, exhibit potent effects on inflammation and immune responses.

Manipulating gut bacteria and their metabolites shows promise in treating metabolic and inflammatory disorders. However, despite advances in gut health and wellness trends, the precise mechanisms governing the immunomodulatory properties of microbe-derived metabolites remain elusive.

To bridge this gap, a team of researchers led by Professor Chiharu Nishiyama from the Tokyo University of Science conducted a series of experiments using both in vitro and in vivo mouse models to understand how bacteria-generated FAs regulate immune responses.

Explaining the rationale behind their work published in *Frontiers in Immunology*, Prof. Nishiyama says, "PUFAs undergo metabolic transformations such as hydroxylation and saturation by enzymes possessed by intestinal bacteria. In recent years, a variety of beneficial physiological effects have been discovered for these intestinal bacterial metabolites.

"In this study, we have investigated the activity of multiple FA metabolites using mouse-derived immune cells."

To this end, the researchers used antigen-stimulated spleen cells to elicit an enhanced immune response. Subsequently, they investigated the impacts of different polyunsaturated fatty acid (PUFA) derivatives,

focusing on metabolites of linoleic acid, a prevalent dietary fatty acid.

Their findings revealed that KetoC, αKetoC, gKetoA, and gKetoC (enon derivatives of LA) markedly reduced the levels of interleukin 2—a key protein that triggers the expansion of immune cells and inflammation. However, the original PUFAs in their unconverted form did not demonstrate the same immunosuppressive effects, emphasizing the critical role of bacterial conversion in activating their immunomodulatory properties.

Furthermore, they observed that the enon (a functional group) FAs also suppressed prolonged T-cell proliferation and dendritic cell activation, which can lead to inflammation and autoimmune diseases. This anti-inflammatory effect was most pronounced with gKetoC. Hence, the researchers aimed to unravel the molecular mechanisms through which gKetoC exerted its immunosuppressive effects.

In addition, previous studies have shown the involvement of G protein-coupled receptors (GPCRs) and the transcription factor, NRF2, in anti-oxidant responses, which are mediated by several FA metabolites, whereas the involvement of GPCRs and NRF2 in the effects of gKetoC in dendritic cells was largely unknown.

To clarify the role of these proteins in gKetoC-mediated immune responses, the researchers assessed the levels of inflammatory cytokines released from antigen-stimulated and gKetoC-treated dendritic cells. Their results suggested that gKetoC stimulated the NRF2 signaling pathway, which suppressed the production of inflammatory cytokines.

Additionally, GPCR-signaling also inhibited inflammatory cytokine production in dendritic cells in an NRF2-dependent manner. This unveils a potential molecular axis governing the immunomodulatory effects of gKetoC.

To further validate their findings in vivo, the researchers used a mouse model of inflammatory bowel disease and examined immune and inflammatory responses by involving gKetoC treatment. They found that gKetoC treatment significantly reduced fibrosis-induced tissue damage in the colon, reduced colitis-induced weight loss, and improved stool scores.

Furthermore, the treated mice showed decreased epithelial cell disruption and ulcers, along with reduced infiltration of immune cells and lower serum levels of inflammatory factors. Notably, the models that were deficient in NRF2 showed significant restoration of colitis-induced tissue damage following gKetoC treatment.

Overall, the present study sheds light on the potential mechanism by which gKetoC alleviates antigen-induced intestinal inflammation. Further studies are needed to understand the complex interplay between gKetoC, GPCR-signaling, and the NRF2 pathway, and uncover other potential targets of gKetoC which mediate its anti-inflammatory effects.

Nevertheless, anti-inflammatory FA metabolites hold therapeutic promise in the treatment of intestinal inflammatory diseases and maintenance of gut health, as prebiotic or probiotic formulations.

Sharing her concluding thoughts, Dr. Nishiyama states, "Our findings demonstrate that the compounds of dietary oils are converted into useful metabolites with anti-inflammatory effects by gut bacteria.

"By conducting detailed analyses at the individual, cellular, and genetic levels, we hope to understand how the food we eat daily influences the function of immune cells, and how these effects can be targeted for the prevention and mitigation of inflammatory diseases."

In summary, while the beneficial effects of bacterial PUFA metabolites

were known, this study identified gKetoC as a metabolite playing a protective role in a colitis mice model. In the long run, these findings can help improve the quality of life for patients suffering from inflammatory diseases, and augment the possibility of developing functional foods, supplements, and nutraceuticals based on these microbial metabolites.

Moreover, the researchers also speculate that these developments could help in the identification and development of compounds that are capable of preventing or alleviating immune-related diseases.

More information: Miki Ando et al, The gut lactic acid bacteria metabolite, 10-oxo-cis-6,trans-11-octadecadienoic acid, suppresses inflammatory bowel disease in mice by modulating the NRF2 pathway and GPCR-signaling, *Frontiers in Immunology* (2024). DOI: 10.3389/fimmu.2024.1374425

Provided by Tokyo University of Science