Health promotion by gut microbial lipid metabolism

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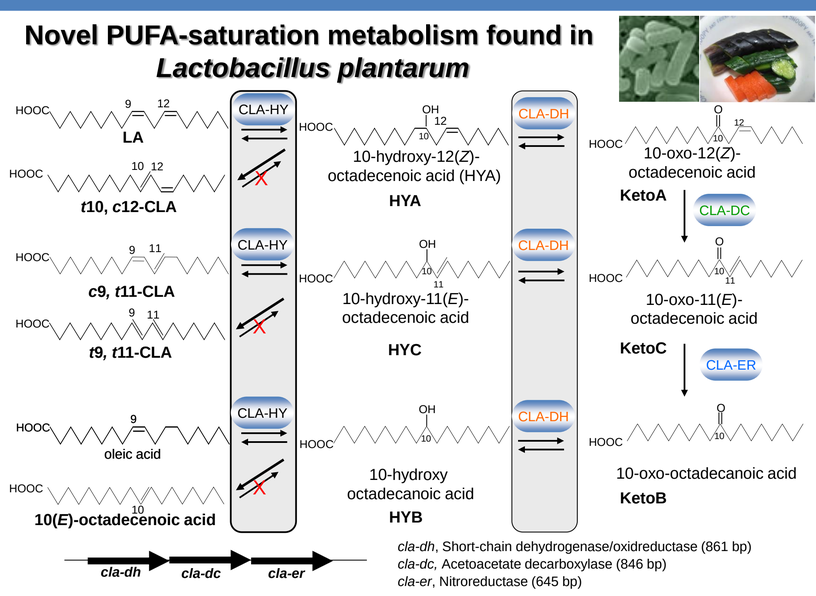
Introduction *(Ref. 1)*

Prevalence of metabolic syndrome has stimulated interest in fat metabolism not only by the host but also by the gut microbiota. We revealed the dietary fatty acid metabolism in representative gut bacteria, lactic acid bacteria, generating hydroxy, oxo, enone, and conjugated fatty acids as intermediates. We confirmed the existence of these fatty acid metabolites in host tissues depending on the existence of gut bacteria and evaluated their physiological activity. For example, a linoleic acid-derived metabolite 10-hydroxy-cis-12-octadecenoic acid (HYA) induced gut hormone, GLP-1, secretion resulted in improving insulin resistance. HYA administration also altered gut microbiome profile bringing increased production of healthy gut microbial fatty acid metabolites. Thus, HYA acted as dual-controller repairing both disease conditions and gut microbial profiles. The effects of HYA was confirmed with human clinical test, then commercialized after development of its efficient microbial production process. HYA was proved to ameliorate sulfate sodium-induced colitis in mice by recovering the damage of intestinal epithelial barrier, and periodontal pathogen-induced gingival epithelial barrier disruption, via GPR40 signaling. Not only HYA, various gut microbial fatty acid metabolites were found to have health-promoting activities. For example, α-Linolenic acid-derived metabolites from gut lactic acid bacteria accumulate M2 macrophage in adipose tissue and repress inflammation. Dietary KetoA intake improved obesity-associated metabolic disorders via up-regulation of adipose tissue function by TRIPVI activation. These results suggested that the dietary fatty acid metabolites by gut microbiota can influence the health of the host. Gut microbial fatty acid metabolites might have potentials as novel functional foods, postbiotics, and pharmaceuticals.

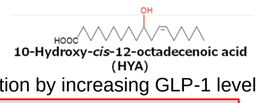
Novel PUFA-saturation metabolism found in *Lactobacillus plantarum*



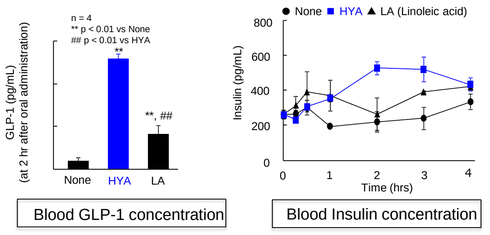
cla-dh, Short-chain dehydrogenase/oxidreductase (861 bp)
cla-dc, Acetoacetate decarboxylase (846 bp)
cla-er, Nitroreductase (645 bp)

Kishino, S. et al, *Proc. Natl. Acad. Sci. USA*, 110, 17808-17813 (2013)

HYA induced gut hormone secretion

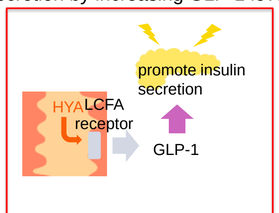


Oral administration of HYA (1000 mg/kg) induces insulin secretion by increasing GLP-1 level



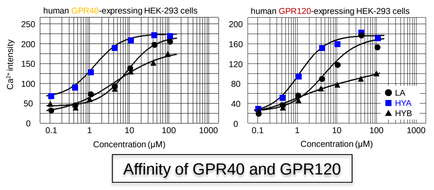
Blood GLP-1 concentration

Blood Insulin concentration



HYA may induce GLP-1 secretion through GPR40, and promote insulin secretion from pancreatic β cells.

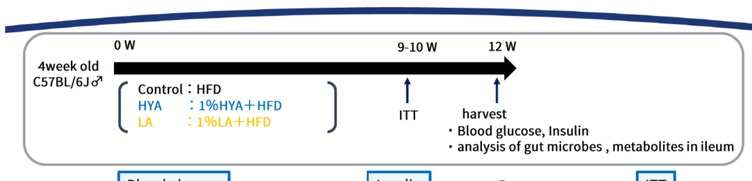
Miyamoto J. The 2016 annual conference of the Japan Society for Bioscience, Biotechnology and Agrochemistry.

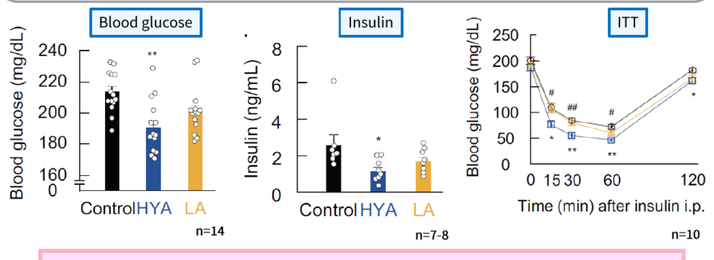


Affinity of GPR40 and GPR120

Miyamoto J., et al, NATURE COMMUNICATIONS 10:4007, 2019

HYA improves insulin resistance



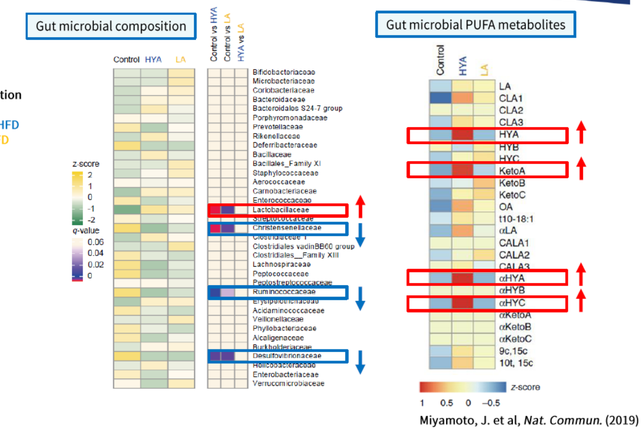


HYA improves HFD-induced insulin resistance by promoting GPR40 and 120-mediated GLP-1 secretion.

Miyamoto J., et al, NATURE COMMUNICATIONS 10:4007, 2019

HYA alters gut microbiome and their metabolites

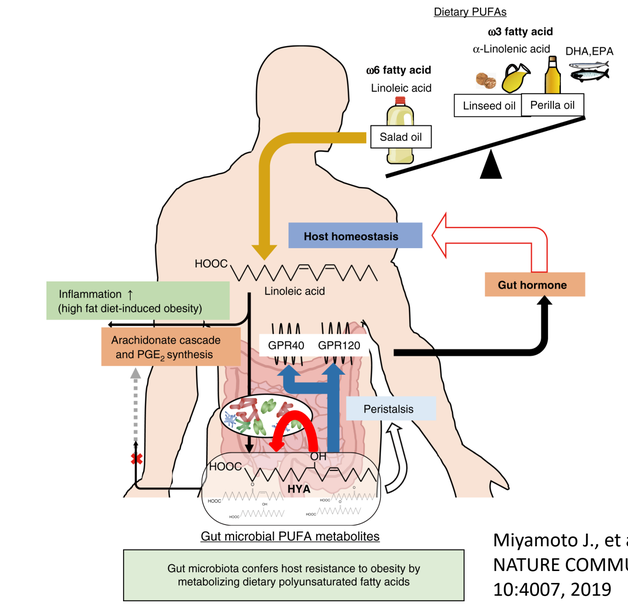
12 weeks administration
Control：HFD
HYA ：1%HYA＋HFD
LA ：1%LA＋HFD



Miyamoto, J. et al, *Nat. Commun.* (2019)

HYA increase the abundance of the *Lactobacillaceae* family and specific metabolites in ileum

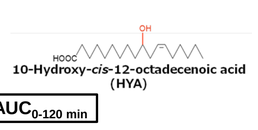
Miyamoto J., et al, NATURE COMMUNICATIONS 10:4007, 2019

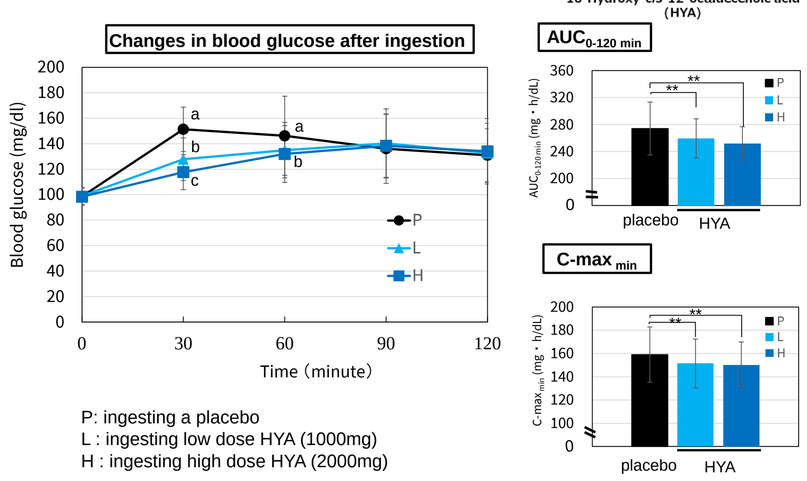


Gut microbiota confers host resistance to obesity by metabolizing dietary polyunsaturated fatty acids

Miyamoto J., et al, NATURE COMMUNICATIONS 10:4007, 2019

Clinical trial results

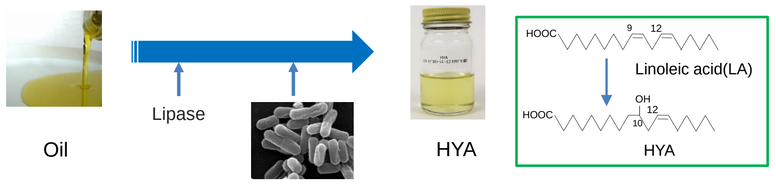




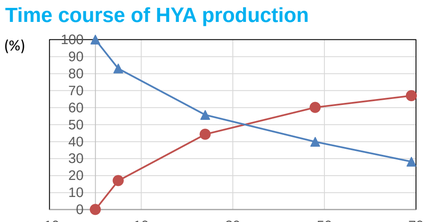
P: ingesting a placebo
L : ingesting low dose HYA (1000mg)
H : ingesting high dose HYA (2000mg)

Yonejima Y., et al, *Prog. Med.*, 37, 1105-1111 (2017)

HYA production from edible plant oils using lactic acid bacteria

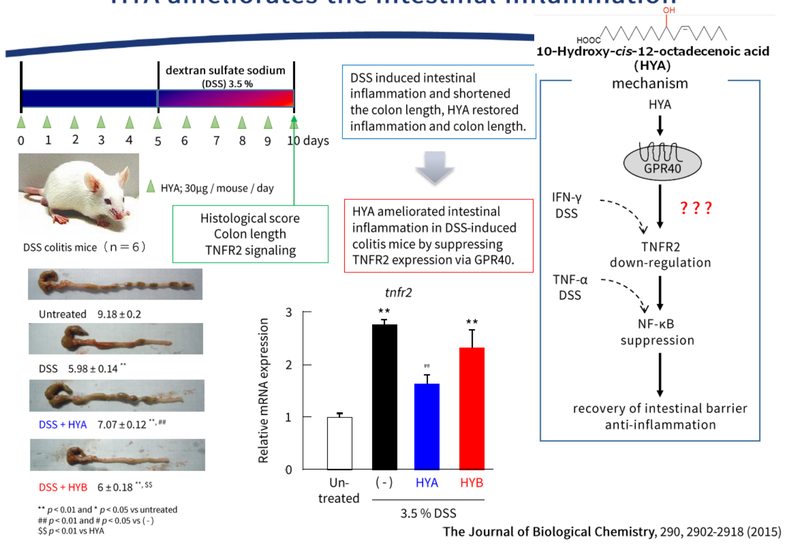


Time course of HYA production



Linoleic acid metabolism in *L. plantarum* AKU1009a

HYA ameliorates the intestinal inflammation

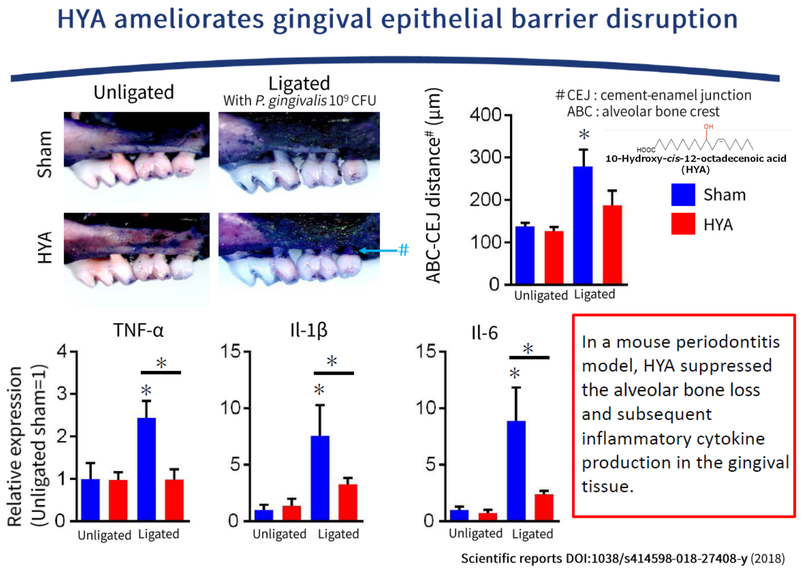


DSS induced intestinal inflammation and shortened the colon length, HYA restored inflammation and colon length.

HYA ameliorated intestinal inflammation in DSS-induced colitis mice by suppressing TNFR2 expression via GPR40.

The Journal of Biological Chemistry, 290, 2902-2918 (2015)

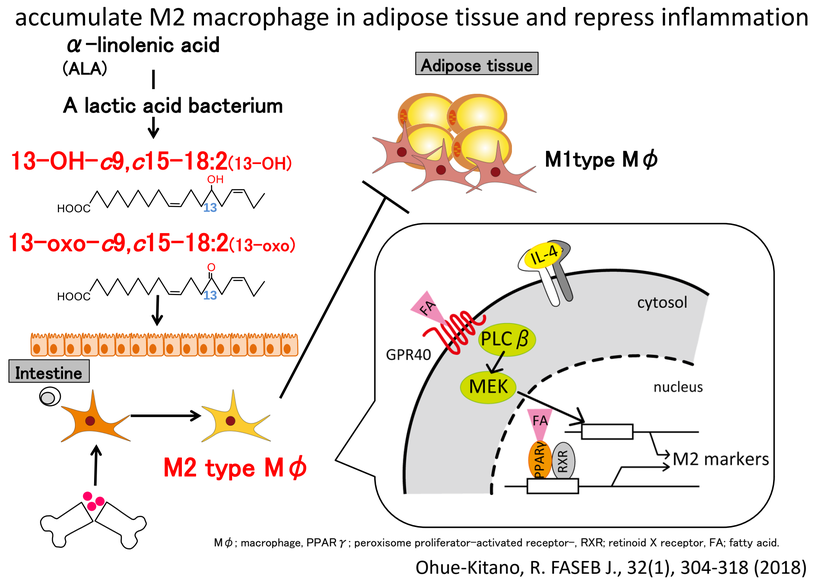
HYA ameliorates gingival epithelial barrier disruption



In a mouse periodontitis model, HYA suppressed the alveolar bone loss and subsequent inflammatory cytokine production in the gingival tissue.

Scientific reports DOI:1038/s414598-018-27408-y (2018)

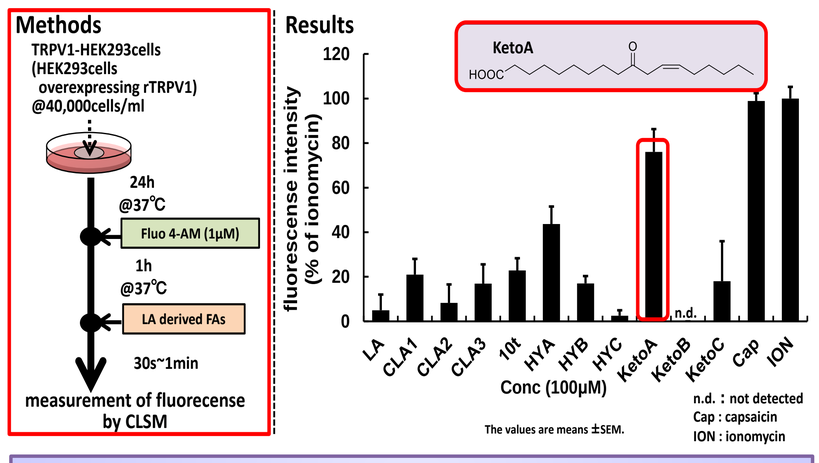
α-Linolenic acid-derived metabolites from gut lactic acid bacteria accumulate M2 macrophage in adipose tissue and repress inflammation



Mϕ; macrophage, PPARγ; peroxisome proliferator−activated receptor−, RXR; retinoid X receptor, FA; fatty acid.

Ohue-Kitano, R. FASEB J., 32(1), 304-318 (2018)

KetoA induced TRPV1-mediated Ca^{2+} influx

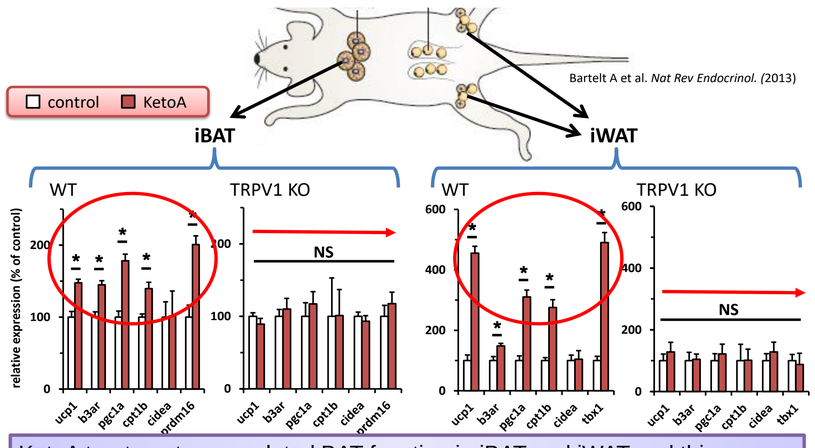


KetoA most potently induced TRPV1-mediated Ca^{2+} influx among the LA-derived various fatty acids.

Kim, M. et al, *FASEB J.*, 31(11),5036-5048 (2017)

KetoA up-regulated genes expression related to BAT function

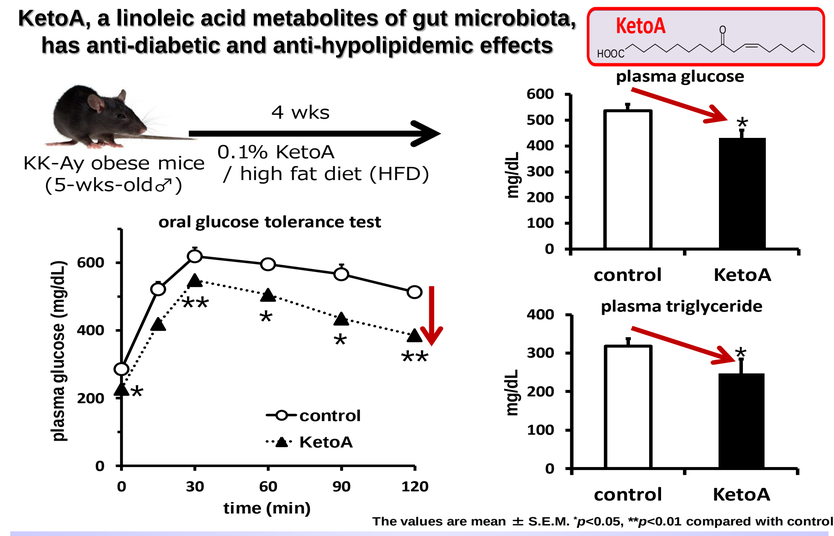
Gene expression in iBAT and iWAT of WT or TRPV1 KO mice treated with KetoA



KetoA treatment up-regulated BAT function in iBAT and iWAT and this function was dependent on TRPV1 activation.

Kim, M. et al, *FASEB J.*, 31(11),5036-5048 (2017)

KetoA, a linoleic acid metabolites of gut microbiota, has anti-diabetic and anti-hypolipidemic effects



The values are mean ± S.E.M. *p<0.05, **p<0.01 compared with control.

Dietary KetoA intake improved obesity-associated metabolic disorders via up-regulation of adipose tissue function by TRIPVI activation.

Kim, M. et al, *FASEB J.*, 31(11),5036-5048 (2017)