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A Gut Microbiota-Generated Metabolite as a Mediator of Healthy Aging

Introduction

Our research explores the crucial roles that gut microbiota-generated metabolites (GMGMs) play at the gut-host axis, impacting both physiological and pathological states. Recently, various groups have demonstrated the beneficial effects of Urolithin A (UA), a novel human mitophagy enhancer, as highlighted in seminal studies published in Nature Medicine (Ryu D et al., 2016) and Nature Metabolism (Andreux PA et al., 2019). Furthermore, two independent double-blind, placebo-controlled randomized clinical trials have shown signs of improvement in mitochondrial and muscular functions (Liu S et al., 2022; Singh A et la., 2022). The promising outcomes of these studies have encouraged our further investigation into GMGMs, aiming to unveil their broader implications for health and longevity.

Methods

Our investigative approach first re-evaluated the role of Lactiplantibacillus plantarum (LAB) GMGMs in mediating LAB-induced longevity, employing both supplementation and conditional media cultured with LABs to assess their effects on lifespan extension in C. elegans. Contrasts were drawn with heat-killed LABs to determine the necessity of live bacteria for the observed benefits. Subsequently, we utilized metabolomics techniques to identify and analyze the presence of phenyllactic acid (PLA), a small molecule produced by LAB, investigating its potential to extend lifespan. Our methodologies were extended to include genetic analysis combined with RNA interference (RNAi) and RNA sequencing (RNA-seq) in nematodes to validate the involvement of the SKN-1/NRF-2 and ATFS-1 signaling pathways in PLA's effects. Additionally, we conducted LC-QTOF analyses to evaluate PLA levels in human plasma with and without sarcopenia.

Results

First, we re-confirmed that LAB supplementation extends lifespan in nematodes. We also discovered that conditional media cultured with LABs can similarly extend lifespan, an effect not observed with heat-killed LABs. This led us to hypothesize that a LAB-generated metabolite mediates the longevity effect. To test our hypothesis, we conducted a metabolomic analysis that identified phenyllactic acid (PLA) as a crucial LAB-generated metabolite promoting lifespan extension, primarily through the SKN-1/NRF-2 and ATFS-1 signaling pathways, as supported by genetic analysis in nematodes. Moreover, in human studies, we observed significantly lower plasma levels of PLA in patients with sarcopenia compared to age-matched non-sarcopenic controls. A notable correlation was also found between plasma PLA levels and muscle performance in the context of sarcopenia, reinforcing our findings in nematodes (Kim J et al., 2023).

Discussion

The outcomes of our research underscore the pivotal role of gut microbiota-produced metabolites, specifically phenyllactic acid, in fostering health and extending lifespan via the SKN-1/NRF-2 and ATFS-1 pathways in nematodes. The association between reduced plasma levels of PLA and sarcopenia in humans highlights the potential relevance of PLA in combating muscle aging, suggesting broader implications for PLA in promoting human health and longevity.

References

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