



# Microbial Genetic Composition Tunes Host Longevity

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## SUMMARY

Homeostasis of the gut microbiota critically influences host health and aging. Developing genetically engineered probiotics holds great promise as a new therapeutic paradigm to promote healthy aging. Here, through screening 3,983 *Escherichia coli* mutants, we discovered that 29 bacterial genes, when deleted, increase longevity in the host *Caenorhabditis elegans*. A dozen of these bacterial mutants also protect the host from age-related progression of tumor growth and amyloid-beta accumulation. Mechanistically, we discovered that five bacterial mutants promote longevity through increased secretion of the polysaccharide colanic acid (CA), which regulates mitochondrial dynamics and unfolded protein response (UPR<sup>mt</sup>) in the host. Purified CA polymers are sufficient to promote longevity via ATFS-1, the host UPR<sup>mt</sup>-responsive transcription factor. Furthermore, the mitochondrial changes and longevity effects induced by CA are conserved across different species. Together, our results identified molecular targets for developing pro-longevity microbes and a bacterial metabolite acting on host mitochondria to promote longevity.

## INTRODUCTION

In large part, because of progress in curing infectious and contagious diseases, modern society is progressively aging and is made up of an ever-growing proportion of elderly individuals. Improving healthy aging and preventing aging-associated chronic disabilities have become a priority of current biomedical research. Although our understanding of aging has been deepened by discoveries of several conserved molecular mechanisms (Kenyon, 2010), few longevity-promoting compounds have been discovered to date (Cabreiro et al., 2013; Harrison et al., 2009, 2014; Howitz et al., 2003).

A growing body of evidence suggests that gut microbiota—diverse microorganisms inhabiting the digestive track—are

tightly linked to the aging process of their host (Cho and Blaser, 2012; Heintz and Mair, 2014). This community of microbial species, among which bacteria are predominant and most extensively studied, not only generates metabolites essential for various host functions (Lee and Hase, 2014) but also mediates effects of exogenous chemicals on the animals they reside in (Cabreiro et al., 2013). Changes in the bacterial composition of the microbiota have been observed in elderly people, and diet-driven microbiota alterations have been shown to improve their health (Claesson et al., 2012; Yatsunenkov et al., 2012). However, most of our knowledge on microbiota is limited to taxonomic and metagenomic profiling, whereas functions of individual microbial genes and their molecular mechanisms in modulating host aging remain elusive. This is due in part to the high complexity of mammalian gut microbiota and to technical challenges of isolating specific pro-longevity microbial variations.

The nematode *Caenorhabditis elegans* with its short and easily monitored lifespan as well as defined microbiota, is a powerful model for disentangling the interactions between microbes and host aging (Heintz and Mair, 2014). Under standard laboratory conditions, *C. elegans* are reared on a single bacterial strain of *Escherichia coli*. Starting from early adulthood of the nematodes, bacterial cells colonize the intestinal lumen and form their entire gut microbiota (Clark and Hodgkin, 2014). Using this simple model system, studies have demonstrated the crucial role that the microbiota play in regulating host longevity (Garigan et al., 2002; Portal-Celhay et al., 2012). Some bacterial variants have been serendipitously identified as determinants of host lifespan (Larsen and Clarke, 2002; Virk et al., 2012), and small molecules secreted from bacteria, such as certain non-coding RNAs and nitric oxide, have been linked to host longevity in the context of specific bacterial backgrounds (Gusarov et al., 2013; Liu et al., 2012). However, a systematic analysis on the longevity-related effects of bacterial genetic factors has not been performed.

In this study, we designed a high-throughput screening platform to identify microbial pro-longevity factors from the entire collection of *E. coli* non-essential gene deletion mutants (Baba et al., 2006). We discovered a series of microbial genetic factors that regulate host health and longevity and demonstrated their interactions with several known aging-regulatory pathways of the host. We also discovered a probiotic mechanism distinct from these known pathways, which functions through induction of a secreted polysaccharide that promotes host longevity by

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