Comparative Biology–Guided Identification of Longevity-Associated Gene Programs and Their Experimental Modulation in Mammalian Aging

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Abstract

Aging acts as a primary risk factor for a wide range of chronic diseases; however, the biological significance of age-associated molecular changes remains highly heterogeneous and poorly understood. While some changes drive functional decline, comparative biology has highlighted that a subset of age-related gene expression shifts resembles transcriptional characteristics observed in long-lived species or strains. This observation raises the critical possibility that specific components of molecular aging may reflect "adaptive," homeostasis-supporting remodeling rather than simple deterioration. In this project, we integrated large-scale transcriptomic datasets from mice and diverse mammalian species to construct a robust atlas of gene sets showing concordant versus discordant relationships between aging-associated changes and longevity-associated profiles. By prioritizing upstream transcriptional regulatory candidates linked to these "concordant" gene programs in metabolic tissues, we identified key drivers of adaptive aging. Furthermore, we established in vivo methods to modulate these selected candidates in a tissue-directed manner in adult mice. Multi-organ molecular profiling following this intervention indicated not only robust local remodeling in the targeted tissue but also suggested broader, systemic-level molecular consequences in remote organs. Together, these results support the feasibility of a comparative biology–driven framework to distinguish potentially adaptive versus maladaptive components of molecular aging, offering a novel strategy to minimize reliance on disease-specific assumptions in aging research.

1. Aim of Research

1-1 Background

With the rapid aging of the global population, extending healthspan requires a mechanistic understanding of aging that goes beyond the conventional "functional decline" model. Traditional aging research has largely relied on comparing young versus old individuals within a single species. However, this approach often fails to distinguish between deleterious changes that cause aging and compensatory responses that attempt to counteract it. Comparative studies across species and strains with different lifespans provide a powerful additional axis to infer longevity-relevant biology. Indeed, recent studies demonstrated that gene expression signatures associated with longer lifespan exhibit significant similarity to those observed during aging across mammals (Takasugi *et al.*, 2023, *Nucleic Acids Res*; Tyshkovskiy et al., 2023, *Cell*). This finding implies that long-lived species possess distinct transcriptional programs that are evolutionarily conserved, and suggests that mimicking these programs could confer homeostatic benefits.

1-2 Objective

The specific objectives of this research were:

(1) To define and validate robust transcriptomic signatures that show concordant (similar-direction) or discordant (opposite-direction) relationships between aging-associated changes and longevity-associated profiles across mammals, thereby isolating "adaptive" signatures;

(2) To identify and prioritize upstream transcriptional regulatory candidates that drive these concordant programs, with a specific focus on metabolic tissues which act as systemic regulators; and

(3) To experimentally establish an in vivo strategy to modulate these selected candidates in adult mice and evaluate the resulting molecular consequences across multiple tissues to test the hypothesis of systemic adaptive remodeling.

2. Method of Research & Progression

2-1 Integrated transcriptomic meta-analysis and cross-species comparison

We collected publicly available RNA-sequencing datasets from multiple cohorts of mice and diverse mammalian species/strains. These were integrated using a rigorous meta-analysis framework to overcome study-specific noise and identify robust aging-associated gene sets. Simultaneously, longevity-associated profiles were derived from datasets linking gene expression with lifespan variation. Genes were then categorized into "concordant" and "discordant" sets based on the vector relationship between their aging-associated directionality and longevity-associated patterns.

2-2 Prioritization of upstream regulatory candidates

To translate these gene lists into mechanistic insights, we performed upstream regulator analysis. We prioritized transcriptional factors whose predicted or annotated target genes were significantly enriched among the "concordant" gene programs. Special emphasis was placed on candidates expressed in metabolic tissues, given their role in systemic energy homeostasis. Selection criteria included reproducibility across datasets, conservation of regulatory motifs, and the feasibility of tissue-directed modulation using viral vectors.

2-3 In vivo tissue-directed modulation and multi-organ profiling

We constructed Adeno-associated virus (AAV) vectors utilizing a tissue-specific promoter to modulate the expression of the selected regulatory candidates specifically in the metabolic tissues of adult mice. Following the intervention period, the targeted tissue and additional remote organs were collected. We performed genome-wide expression profiling (transcriptomics) and complementary molecular assessments to evaluate the extent of local remodeling and to explore potential systemic-level molecular consequences, specifically looking for the suppression of aging signatures in non-targeted tissues.

3. Results of Research

3-1 Robust definition of concordant and discordant gene programs linked to longevity

Across multiple independent datasets, we successfully established a statistically supported framework to classify aging-associated genes. We found that "concordant" gene programs—those shared between aging and longevity models—were significantly enriched for metabolic and homeostasis-related processes. This result provides strong computational evidence supporting the hypothesis that a subset of molecular aging represents an adaptive shift toward a state resembling that of long-lived animals.

3-2 Identification of regulatory candidates associated with concordant programs

Our upstream analysis highlighted a discrete set of transcriptional regulatory candidates. The target gene sets of these regulators were consistently overrepresented among the concordant programs in metabolic tissues. These candidates were thus prioritized as putative "master regulators" of longevity-associated, adaptive-like remodeling, capable of orchestrating complex metabolic shifts.

3-3 Evidence of multi-tissue molecular consequences via local modulation

By establishing an in vivo pipeline for tissue-

directed modulation, we confirmed that manipulating these candidates induced robust molecular remodeling in the targeted tissue, mimicking the "adaptive" profile. Most notably, multi-organ transcriptomic profiling revealed that this local intervention was accompanied by beneficial molecular consequences in remote, non-targeted tissues. This suggests that the induced adaptive state in the metabolic organ triggered inter-organ communication signals, leading to a systemic attenuation of age-associated transcriptional signatures. Detailed organ-specific outcomes and the identity of the regulators are being reserved for peer-reviewed publication to protect the novelty of these findings.

4. Future Area to Take Note of, and Going Forward

This study has opened new avenues for understanding systemic aging networks. Future work will focus on: (1) refining the causal hierarchy between the prioritized regulators and concordant gene programs using complementary gain- and loss-of-function approaches; (2) identifying the specific circulating mediators (e.g., metabolites or hepatokines) that connect tissue-local remodeling to the observed systemic molecular states; and (3) evaluating how these molecular pathways relate to physiological phenotypes relevant to healthspan. This line of research contributes to a principled strategy for separating adaptive versus maladaptive components of aging, potentially leading to interventions that preserve homeostatic programs.

5. Means of Official Announcement of Research Results

The results are currently being compiled into a manuscript for submission to a high-impact international peer-reviewed journal. We plan to present the findings at relevant scientific meetings following the acceptance of the paper. All publications and presentations will gratefully acknowledge the support from the Mitsui Sumitomo Insurance Welfare Foundation.

6.References

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2 Tyshkovskiy, A. et al. Distinct longevity mechanisms across and within species and their association with aging. Cell 186, 2929-2949.e2920 (2023). https://doi.org/10.1016/j.cell.2023.05.002