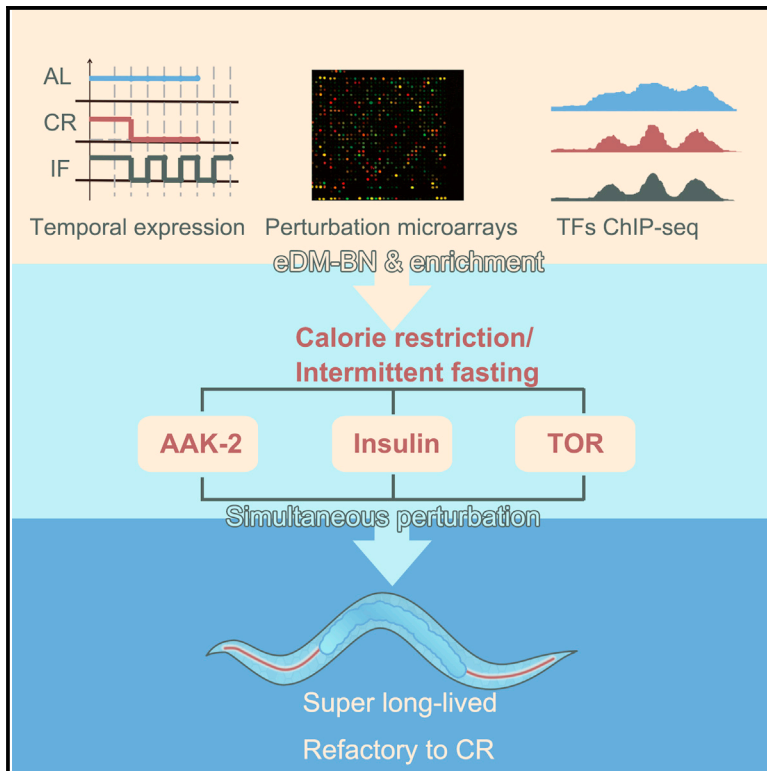# A Systems Approach to Reverse Engineer Lifespan Extension by Dietary Restriction

Graphical Abstract

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In Brief

Hou et al. used unbiased systems approaches to identify novel regulatory networks for dietary restriction in *C. elegans*. They uncover three transcriptomic modules, which, when simultaneously targeted, result in extremely long-lived animals refractory to dietary restriction. This innovative reverse engineering approach highlights the extensive feedback controls underlying aging.

Highlights

- We obtain temporally resolved effects of diet restriction on aging transcriptomes

- Early responses involve metabolism; late involve cell cycle and DNA damage

- We find three regulator groups with novel regulators separated by target specificity

- Regulator feedbacks are leveraged to fully recapitulate diet restriction effects

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A Systems Approach to Reverse Engineer Lifespan Extension by Dietary Restriction

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SUMMARY

Dietary restriction (DR) is the most powerful natural means to extend lifespan. Although several genes can mediate responses to alternate DR regimens, no single genetic intervention has recapitulated the full effects of DR, and no unified system is known for different DR regimens. Here we obtain temporally resolved transcriptomes during calorie restriction and intermittent fasting in *Caenorhabditis elegans* and find that early and late responses involve metabolism and cell cycle/DNA damage, respectively. We uncover three network modules of DR regulators by their target specificity. By genetic manipulations of nodes representing discrete modules, we induce transcriptomes that progressively resemble DR as multiple nodes are perturbed. Targeting all three nodes simultaneously results in extremely long-lived animals that are refractory to DR. These results and dynamic simulations demonstrate that extensive feedback controls among regulators may be leveraged to drive the regulatory circuitry to a younger steady state, recapitulating the full effect of DR.

INTRODUCTION

Dietary restriction (DR) induces lifespan extension in yeast, worms, flies, mice, and monkeys (Fontana et al., 2010; Kenyon, 2010). Several key signaling pathways and regulators have been identified that partially mediate the effects of DR on aging and lifespan, such as insulin/IGF1-like growth factor signaling pathway, AMPK signaling pathway, TOR signaling pathway, and the sirtuin protein family (Kenyon, 2010). However, none of these pathways are solely responsible for the DR effect, because

blocking any of them individually does not fully block DR-induced lifespan extension by all regimens. Thus, although targeting these pathways results in long-lived animals, DR still gives additional benefits. It remains unclear whether different pathways mediate different aspects of DR response, whether they interact with each other in response to DR, or whether they act at different stages of DR.

DR is known to induce systemic changes in a whole organism (Lee et al., 1999; Pletcher et al., 2002; Zhou et al., 2012) and is therefore a good paradigm to learn how regulation of aging can be achieved at the systems level. Previously we compared the midlife liver transcriptome changes induced by caloric restriction or exercise on high-fat- or low-fat-diet mice and identified molecular pathways that correlate with the mean lifespans across different regimens (Zhou et al., 2012). However, transcriptomic analyses of one time point are not sufficient to resolve the cause versus consequence of DR effects, where early starvation signaling must be converted or relayed to late aging regulators to induce long-term health benefits.

Here, using *C. elegans* as a model, we analyzed the temporal profiles of two DR regimens, calorie restriction (CR) and intermittent fasting (IF), to identify early and late gene expression responses to CR and IF, and computationally inferred potential regulators for these responses. We found that early response genes are more significantly changed at the transcriptional level compared to late response genes, and known lifespan regulators tend to display a postreproduction stage reversal of gene expression patterns. Furthermore, we inferred three regulatory modules according to their activity or target profiles: (1) an *rheb-1_let-363/tor* module that targets very early response genes involved in metabolism, (2) an *aak-2_tax-6_xbp-1* module that is rapidly upregulated in response to starvation and represses age-dependent increases in phosphorylation and dephosphorylation processes, and (3) a module containing *daf-16* and *glp-1* and their target transcription factors (TFs) that delay the postreproduction increase in DNA damage response gene expression. Based on these regulatory patterns and the intensive feedback controls between different regulators, we