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Intermittent time-restricted feeding promotes longevity through circadian autophagy

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ABSTRACT

Macroautophagy/autophagy plays crucial roles in aging and the pathogenesis of age-related diseases. Studies in various animal models demonstrate the conserved requirement for autophagy-related genes in multiple anti-aging interventions. A recent study from the Shirasu-Hiza lab showed that a newly designed intermittent time-restricted feeding (iTRF) dietary regimen can robustly extend fly healthspan and lifespan through circadian rhythm-dependent activation of autophagy. The night-specific induction of autophagy is both necessary and sufficient for iTRF-mediated health benefits. The study provides the intriguing possibility that novel behavioral or pharmaceutical interventions that promote night-specific autophagy can be used to promote healthy aging.

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Aging is a chronological, multifaceted process characterized by the progressive functional decline of every tissue and organ; it is the source of most chronic diseases including heart disease, diabetes, cancer, and neurodegenerative diseases, and the main burden for healthcare in developed countries [1]. Therefore, it is of paramount importance to understand the molecular and cellular mechanisms of aging and aging-associated diseases and identify interventions that promote healthy aging.

One pathway found to have anti-aging effects across species is autophagy, a highly conserved lysosomal degradation process that is essential for cellular homeostasis. Different lines of evidence have revealed the relationship between aging and autophagy including: (1) autophagy declines with age; (2) multiple autophagy-related genes and autophagy are required for organismal longevity; and (3) increased autophagy is beneficial to lifespan extension [2,3]. Several interventions that delay aging, including calorie restriction, genetic manipulation, and pharmaceutical administration such as the use of MTOR inhibitors and spermidine, are mediated through autophagy activation, which establishes autophagy as a fundamental mechanism in anti-aging [2,4].

Time restricted feeding (TRF), in which food intake is restricted to certain hours of the day (usually within 12 h) without altering calorie consumption, has gained a lot of attention as a potential anti-aging intervention. TRF provides many health benefits including protecting against metabolic disease and reducing risk of age-related disease in animal models and humans [5,6]. However, it is not clear whether TRF can delay aging and what molecular mechanisms underlie the TRF-related health benefits.

The article recently published by Ulgherait et al. in *Nature* and highlighted here tested different feeding and fasting regimens, including 24-h feed (ad libitum), 24-h intermittent fasting (IF), 12-h feed during lights on and 12-h fasting during lights off (TRF), and 20-h fasting 28-h feed in which fasting starts at 6 h after lights on (intermittent TRF), and found that iTRF significantly extends *Drosophila* lifespan [7]. This iTRF-mediated lifespan extension is independent of caloric restriction, dietary protein restriction and inhibition of insulin-like signaling, factors known to promote autophagy and longevity. The extended lifespan might result from increased healthspan and delayed aging because flies on iTRF exhibit improvement in multiple aging parameters such as climbing ability, aging-related protein aggregation, and intestinal aging markers.

Because iTRF differs from other feeding regimens in the timing of food intake but not diet composition, the authors asked whether circadian clock genes are involved. Similar to previous reports on TRF regimens, iTRF enhances circadian gene expression. In mutant flies with a disrupted circadian clock, iTRF is no longer able to extend lifespan and healthspan, indicating that a functional circadian clock is required for the health benefits of iTRF. Furthermore, when the iTRF schedule is shifted by 12 h so the fasting happens during daytime, iTRF-mediated benefits are also abolished, suggesting the necessity of night-biased fasting for iTRF to exert its function.

How does iTRF induce longevity through circadian genes? The authors examined the role of autophagy in iTRF, for the reasons that (1) iTRF involves fasting; (2) autophagy will be induced and plays essential roles in response to starvation; (3) autophagy is also rhythmically activated [8]. They first showed that, two essential autophagy genes *Atg1* and *Atg8a* are circadian regulated, with expression peaking at night, overlapping with nighttime fasting. iTRF can increase the

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expression of both genes in a circadian gene-dependent manner. In line with the increased autophagy gene expression, iTRF leads to high levels of autophagy activity in flies with intact circadian rhythm. RNAi knockdown of either Atg1 or Atg8a prevent iTRF from extending lifespan, indicating that autophagy is required for iTRF-mediated benefits.

To further demonstrate the role of "circadian autophagy", the authors manipulated the timing of autophagy gene expression using both genetic and pharmacological tools. Knockdown of night-specific Atg1 and Atg8a expression leads to a similar phenotype as general RNAi knockdown, confirming the necessity of circadian upregulation of autophagy genes. Night-specific overexpression of Atg1 or Atg8a promotes the lifespan of flies on the ad libitum diet to as long as the flies on iTRF and does not cause any further lifespan extension for flies already on iTRF, suggesting that circadian-regulated autophagy is sufficient for lifespan extension and is the major driver of iTRF-mediated benefits. By contrast, day-specific fasting or autophagy induction fail to extend lifespan.

Taken together, Ulgherait and colleagues showed that circadian-regulated upregulation of autophagy specifically at night is not only required but is also sufficient for iTRF-induced healthspan and lifespan extension. The study provided evidence to support applying iTRF as a possible dietary approach for health benefits. Because iTRF is independent of conventional anti-aging strategies such as calorie restriction and insulin signaling inhibition, it has the potential to be combined with other strategies for a better improvement in health indices. Further study may seek to identify applicable drugs to induce night-specific autophagy to mimic the effects and benefits of iTRF.

There are also many questions related to autophagy that need to be addressed. Circadian autophagy is found in many different organs; however, the activation and oscillation of autophagy in different organs are not synchronized. This raises the question as to what tissues and organs display enhanced autophagy in response to iTRF. In the current study, the authors induced autophagy by overexpressing Atg1 or Atg8a, which are essential for both nonselective and selective autophagy. Considering that these processes including mitophagy, lipophagy, aggrephagy and lysophagy play different beneficial roles in aging and age-related diseases [3], it is of great importance to understand what type(s) of autophagy and cargo is involved in iTRF-mediated health benefits. The molecular mechanisms by which circadian autophagy promotes healthspan also requires further research.

Upregulation of autophagy is the underlying mechanism of many interventions that promote longevity including iTRF. However, there seems to be a threshold or healthy range that determines whether the increased autophagy is life-beneficial or life-detrimental. A recent study in flies showed that mild Atg1 upregulation and autophagy extends lifespan whereas strong Atg1 overexpression leads to reduced mitochondrial metabolism and shortened lifespan, indicating the importance of fine-tuning autophagy to optimal levels [9]. Therefore, further in-depth studies are required to understand to what extent autophagy is upregulated in iTRF and how to induce autophagy to the appropriate levels at the right place and right time to mimic iTRF.

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References

[1] Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006;367:1747–1757.
[2] Aman Y, Schmauck-Medina T, Hansen M, et al. Autophagy in healthy aging and disease. Nat Ageing. 2021;1:634–650.
[3] Hansen M, Rubinsztein DC, Walker DW. Autophagy as a promoter of longevity: insights from model organisms. Nat Rev Mol Cell Biol. 2018;19:579–593.
[4] Campisi J, Kapahi P, Lithgow GJ, et al. From discoveries in ageing research to therapeutics for healthy ageing. Nature. 2019;571:183–192.
[5] Rothschild J, Hoddy KK, Jambazian P, et al. Time-restricted feeding and risk of metabolic disease: a review of human and animal studies. Nutr Rev. 2014;72:308–318.
[6] Longo VD, Panda S. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. Cell Metab. 2016;23:1048–1059.
[7] Ulgherait M, Midoun AM, Park SJ, et al. Circadian autophagy drives iTRF-mediated longevity. Nature. 2021;598:353–358.
[8] Ma D, Li S, Molusky MM, et al. Circadian autophagy rhythm: a link between clock and metabolism? Trends Endocrinol Metab. 2012;23:319–325.
[9] Bjedov I, Cocheme HM, Foley A, et al. Fine-tuning autophagy maximises lifespan and is associated with changes in mitochondrial gene expression in Drosophila. PLoS Genet. 2020;16:e1009083.