Towards healthy aging:

Identifying molecular pathways regulated by caloric and temporal restriction as critical feeding factors to extend lifespan

Caloric restriction (CR) extends lifespan in several organisms, including non-human primates, yet the mechanisms remain unknown. Traditional CR protocols lead to a profound temporal restriction (TR) in feeding behavior, which by itself has critical effects on health. Thus, it is possible that the benefits of caloric restriction may arise from the temporal restriction of food intake, rather than the reduction in calories itself.

To address this, we developed an automated feeder system that controls duration, amount and timing of food availability, and records feeding and voluntary wheel-running activity in mice. Using this system, mice were exposed to temporal or caloric restriction protocols. Mice under CR consolidated their intake within 2h, thereby self-imposing a temporal restriction of food consumption. Interestingly, even under CR, mice eating at the “wrong” time of the day gained more weight than mice fed exclusively during their normal active phase at night.

By RNA-seq, we found that TR and CR have complex genome-wide effects on the circadian transcriptome in the liver of young mice. Key aging pathways are particularly affected; displaying large shifts in their 24h rhythmic patterns of gene expression, including insulin and mTOR signaling and ubiquitin-mediated proteolysis. Since circadian rhythms with low amplitude or incorrect phase of expression are hallmarks of aging, such “circadian misalignment” could be contributing to aging.

In conclusion, we have determined short-term behavioral, metabolic and molecular adaptation to different feeding conditions. The next question to explore is whether the amount or the timing of food intake are able to improve circadian metabolism, delay the onset of age-related diseases and eventually extend lifespan in mammals.

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