Nature Reviews Molecular Cell Biology | Published online 21 Apr 2017; doi:10.1038/nrm.2017.45

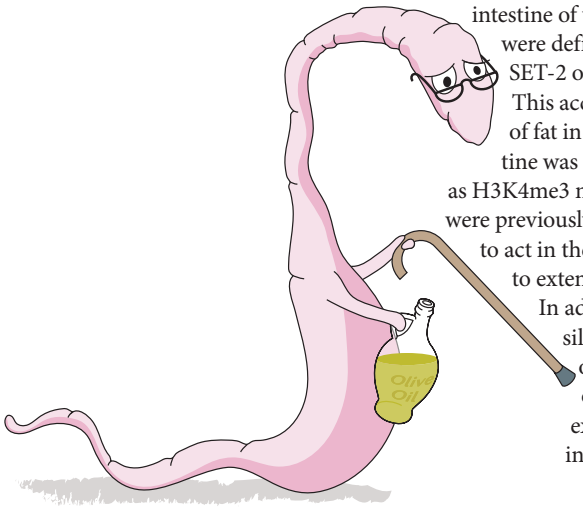
AGEING

Is fat a key to longevity?

Fat metabolism has a crucial role in several physiological and pathological processes, and has been associated with changes in lifespan. It is also known that chromatin states and chromatin modifiers regulate lifespan in several species, but how chromatin and metabolic states are connected and how they affect longevity are poorly understood. Brunet and colleagues now report that a deficiency in the COMPASS chromatin complex — which catalyses trimethylation of histone H3 Lys4 (H3K4me3) — leads to the accumulation of monounsaturated fatty acids (MUFAs) in the intestine of the worm *Caenorhabditis elegans* and that this extends the lifespan of the animal.

The authors set out to investigate whether known chromatin modifiers can induce metabolic changes, and focused on the *C. elegans* COMPASS chromatin complex, as it had been shown previously that worms deficient in the COMPASS components ASH-2 and SET-2 are long-lived, suggesting a role for H3K4me3 alterations in modulating organismal fitness. Staining and biochemical analyses of fat species revealed that triglycerides accumulated in the intestine of worms that were deficient in SET-2 or ASH-2. This accumulation of fat in the intestine was surprising, as H3K4me3 modifiers were previously reported to act in the germline to extend lifespan. In addition, silencing of *ash-2* or *set-2* expression in the intestine did not promote fat accumulation or lifespan extension, confirming that COMPASS functions outside the intestine to regulate fat accumulation, and suggesting the existence of a communication mechanism between the germline and the intestine.

> “accumulation of monounsaturated fatty acids … extends the lifespan”



When profiling fatty acids, the authors found that *ash-2* knockdown increased MUFAs, but not saturated fatty acids or polyunsaturated fatty acids, indicating that COMPASS specifically influences MUFA metabolism. Furthermore, upon *ash-2* knockdown, *fat-5* and *fat-7*, which encode delta-9 fatty acid desaturases (involved in MUFA synthesis), were upregulated in the intestine. Further analyses indicated that the switch to MUFA metabolism that is induced by COMPASS deficiency is driven by *fat-7* upregulation in the intestine.

So what are the mechanisms underlying the germline–intestine communication? Using transcriptomic analyses, the authors identified seven potential COMPASS target genes that were substantially downregulated upon *ash-2* knockdown. One of them, *rsks-1*, was downregulated in the germline, which led to intestinal *fat-7* upregulation, increased MUFA levels and fat accumulation. This finding was consistent with previous reports indicating that RSKS-1 and its mammalian homologue S6 kinase promote fat accumulation in *C. elegans* and lifespan extension in *C. elegans* and mice. Next, the authors found that MUFA accumulation in COMPASS-deficient worms is dependent on a highly conserved transcriptional network that controls delta-9 fatty acid desaturase gene transcription. Interestingly, this network is crucial for the long lifespan of COMPASS-deficient worms, suggesting that MUFA accumulation is necessary for lifespan extension. Thus, these data suggest that COMPASS regulates the germline expression of RSKS-1, the activity of which mediates (at least in part) the nuclear accumulation of transcription factors that upregulate the delta-9 desaturase FAT-7 in the intestine, and thus MUFA accumulation and lifespan extension. However, the mechanisms that connect RSKS-1 in the germline to transcription factor activity in the intestine remain to be identified.

Last, the shortened lifespan of worms that are deficient for both COMPASS and FAT-7 could be extended by supplementing their diet with oleic acid (a dietary MUFA), confirming that MUFAs have a key role in promoting longevity in H3K4me3 methyltransferase-deficient animals. Interestingly, giving oleic acid and other MUFAs as dietary supplements was sufficient to increase longevity even in physiological conditions.

This study provides new insights into the links between epigenetic changes, fat metabolism and longevity. Although the mechanisms by which MUFAs extend lifespan remain to be unravelled, the conservation between worms and mammals of factors regulating lipid metabolism raises the intriguing possibility that these fats may be beneficial for lifespan in different species.

Kim Baumann

ORIGINAL ARTICLE Han, S. *et al.* Monounsaturated fatty acids link H3K4me3 modifiers to *C. elegans* lifespan. *Nature* http://dx.doi.org/10.1038/nature21686 (2017)
FURTHER READING Benayoun, B. A., Pollina, E. A. & Brunet, A. Epigenetic regulation of ageing: linking environmental inputs to genomic stability. *Nat. Rev. Mol. Cell Biol.* **16**, 593–610 (2017)