Epigenetic control of lipid metabolism: implications for lifespan and healthspan

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Improvements in prevention and treatment of cardiovascular diseases (CVD) have resulted in a meaningful decline in cardiovascular mortality and increased life expectancy in industrialized countries. However, aging of the global population, coupled with the success of cardiovascular prevention and therapeutic intervention, have culminated in increasing prevalence of chronic heart disease. Thus, we have witnessed over the last 40 years a progressive shift in the delicate balance between lifespan and healthspan. Aging is one of the most powerful disease risk factors, especially for CVD. In contrast with other risk factors, such as high blood pressure or smoking, aging is a ‘non-modifiable’ risk factor. This implies that nothing can be done to arrest senescence. Despite this, considerable effort has been directed at slowing the aging process. Indeed, a number of interventions in preclinical and clinical settings have been proposed to increase lifespan.

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Commentary on ‘Mono-unsaturated fatty acids link H3K4me3 modifiers to C. elegans lifespan’ by Han et al., Nature 2017.1

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The global epidemic of obesity remains among the greatest contemporary challenges in cardiovascular medicine. Obesity has powerfully detrimental effects on cardiovascular health. That said, the association between fat and cardiovascular risk has not been fully elucidated. Epidemiological studies have shown that excess body mass index (BMI) is associated with substantially shorter healthy lifespan. Although, BMI is the most commonly used parameter to gauge adiposity, limitations in its interpretation are well established. Interestingly, fat accumulation increases lifespan in invertebrates and lower mammals. However, how lipids influence lifespan remains unclear.

Epigenetic regulation is a major mechanism governing numerous cellular processes. Histone modifications are susceptible to metabolic changes, as most of the enzymes involved in chromatin remodelling use metabolic substrates as cofactors. For example, α-ketoglutarate, an intermediate of the Kreb’s cycle, is required for the function of certain histone methyltransferases as well as cytosine hydroxylation, a reaction mediated by TET (ten eleven translocation) enzymes. Given the robust relationship between metabolic changes and epigenetic control, attempts have been made to decipher how these processes influence each other. Recent work by Han et al. provides compelling insights into how lipid metabolism, histone methylation, and lifespan are intricately linked.

Trimethylation (m3) of lysine 3 (K3) on histone 4 (H4) (H4K3me3) is an epigenetic mark indicative of active chromatin sites; it is associated with increased accessibility of chromatins structure and consequent increases in transcription. In worms and mammals, loss of function of H4K3 methyltransferase is associated with increased lifespan. In the present study, the authors discovered that inactivation of the H4K3 methyltransferase complex in worms positively influences fat deposition and increases fat storage. In search of the specific lipid class that accumulates, the authors identified the accretion of mono-unsaturated fatty acids (MUFAs) as a specific lipid signature in long-lived worms. Accumulation of MUFAs in H4K3 methyltransferase-deficient worms was dependent on specific upregulation of FAT7, a MUFA synthetic enzyme, suggesting that modification of the H3K4 methylation landscape impacts lipid metabolism. Going forward, the investigators were able to show that H3K4me3 methyltransferase deficiency in worms leads to reduction in RSKS-1 (homologue of mammalian S6 kinase), a key and highly conserved substrate of mTORC1 (mechanistic target of rapamycin complex 1). RSKS-1 deficiency promoted lipid deposition in worms and extended lifespan in mice and Caenorhabditis elegans. Using several elegant genetic tools, Han and collaborators demonstrated that rsk-1 mediates the lipid metabolic switch to MUFAs in H3K4me3-deficient worms. Finally, supplementation with MUFA, but not with the downstream polyunsaturated fatty acids (PUFAs), extended lifespan in worms despite the fact that both types of lipid induce a high-fat phenotype.

Although the findings presented in this paper suggest that ‘fat’ worms live longer, it is important to note that the quality of fat source appears to be more important than lipid per se. Indeed, only MUFA supplementation extended lifespan. Oleic acid, one of the MUFAs, is the predominant fatty acid in olive oil. Strikingly, robust epidemiological evidence has shown that chronic exposure to Mediterranean diet (rich in olive oil) is associated with decreases in CVD and increased life expectancy. What are the mechanisms whereby the Mediterranean diet confers cardioprotection? Are MUFAs the most important mediators? First, a note of caution is warranted. Significant discrepancy has been noted between epidemiological and preclinical studies, as MUFA-rich diets promote atherosclerosis in animal models. Direct measurements of the burden of atherosclerosis in MUFA-fed mice and non-human pri- mates have consistently shown that MUFA-enriched diets increased low-density lipoprotein (LDL) levels due to the actions of the hepatic cholesterol esterifying enzyme ACAT2 (acyl-coenzyme A: cholesterol acyltransferase 2), driving atherosclerosis progression. Therefore, it is unlikely that the atheroprotective effects of the Mediterranean diet derive from consumption of a high quantity of MUFAs and but rather other dietary components likely contribute. This suggests that multiple, yet-to-be-discovered, pathways orchestrate the impact of dietary components on cardiovascular health.

Whereas dietary factors clearly play a major role in increasing healthspan and lifespan in countries encircling the Mediterranean Sea, less is known about epigenetic modifications that may exist and interact with the environment in a healthy elderly population. In the paper by Han et al., histone methylation modifiers influence MUFA metabolism, and the protective effects of these lipids occur either when endogenous synthesis is boosted by epigenetic regulation or when MUFAs are supplemented from exogenous sources. This raises the tantalizing prospect that epigenetic regulation of lipid metabolism switched toward MUFA production can be achieved using specific demethylating agents.

Virtually every epigenetic modification occurring at specific loci has been implicated in the governance of the expression of genes involved in lipid metabolism and possibly even in metabolic diseases. In fact, epigenetic regulation of gene expression is quite complex. The integration of multiple different ‘omics’ approaches (epigenomics, transcriptomics, etc.), coupled with detailed disease phenotyping and robust bioinformatics platforms, will be required to develop a comprehensive understanding of how epigenetic modifications of gene expression influence disease pathophysiology. And it is worth emphasizing that harnessing this potential will require significant focus on ‘big data’; as such, collaborative approaches and data sharing across the scientific community will be required.

Philosophically, what should the ultimate goal of cardiovascular research entail—increasing healthspan or increasing lifespan? The term lifespan does not necessarily take into account quality of life and does not imply a disease-free state. Likely, this derives in part from reliance on preclinical models in which measuring length of life represents an easier experimental benchmark compared to the evaluation of health. However, discovery of molecular mechanisms associated with aging and novel molecular targets associated with delayed aging may ultimately have important implications in altering the disease state. Indeed, interventions that extend lifespan can also increase healthspan, reducing the morbidity of specific diseases. For example, nutrient-sensing mutations in C. elegans that extend lifespan also induce tumour resistance. Dietary restriction, the best known longevity-promoting intervention, positively impacts healthspan in a numbers of ways. However, prolonging lifespan and disease resistance do not always correlate, suggesting that specific pathways are involved in the determination of the two processes.

Alterations in the mTOR nutrient-sensing signalling pathway have been associated with aging, metabolic stress, and CVD. Autophagy is among the most evolutionary conserved mechanisms of stress responsiveness regulated by mTOR, and its modulation has been implicated in CVD. In the presence of nutrients, mTOR is activated, and autophagy is suppressed. Suppression of mTOR by caloric restriction leads to increasing autophagy which has been associated with longevity. Inhibition of H3K4 methylation reduces mTOR activity, suggesting that activation of autophagy may be a supplementary mechanism contributing to increased lifespan in these worms. Future work is needed to solve the autophagy/longevity/epigenetic conundrum.
Convergence of signaling pathways that govern lifespan and disease suggests that enhanced understanding of mechanisms promoting longevity will uncover novel therapeutic targets. Epigenetics is among the most exciting areas of cardiovascular research, and discovery of epigenetic regulatory mechanisms of longevity will be an important step forward in the biology of CVD.

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References