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Editorial

Epigenetic Clock: A Novel Tool for Nutrition Studies of Healthy Ageing

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Epigenetic regulation includes a set of regulatory processes, such as histone modification, DNA methylation and small noncoding RNA regulation, which modify gene expression without changing its original DNA sequence (1). Among all the epigenetic modifications, DNA methylation has been extensively studied in the past decades. DNA methylation mainly refers to the covalent addition of methyl groups to the 5' position of a cytosine. Such process is catalysed by DNA methyl transferases (DNMTs) and mainly occurs at cytosine-phosphate-guanine (CpG) sites in the human genome (2). The function of DNA methylation varies with the location it takes place within the genome. Usually, gene expression is repressed with elevated DNA methylation levels in promoters while gene body methylation is linked with upregulated transcription (3). The removal of methyl groups (i.e., DNA demethylation) can happen either passively by failing to maintain the methylation patterns after replication or actively through oxidizing methylated cytosine into 5-hydroxymethylcytosine (5-hmC), a process mediated by ten-eleven translocation (TET) enzymes (4).

DNA methylation is a dynamic process that progressively diverges across lifetime. Heyn et al. compared peripheral blood DNA methylation patterns of newborns and centenarians, and reported a globally decreased methylation level in the centenarian while in gene promoters of the aged group, the methylation level was higher than the newborn (5). The study of Kananen et al. on blood methylation patterns of a middle-aged population (40-49 years) identified 1,202 ageing-associated CpG sites (6), the majority (987 sites) of which were also found in a methylation comparison between young adults and nonagenarians (7). Besides blood, age-related CpG sites have been uncovered from other tissues such as saliva (8), skeletal muscle (9) and brain (10). The discovery of age-related CpG sites provides a novel approach for age prediction. In the year 2011, Bocklandt et al. pioneered such prediction by building a regression model, which explained 73% of the variance in age, based on two CpG sites identified from saliva (8). Two years later, Horvath introduced an epigenetic clock, also known as DNA methylation (DNAm) age, based on 353 CpG sites identified across 51 tissues with a median absolute prediction error of 3.6 years (11). Despite that other epigenetic clocks have been continuously created (10, 12–14), Horvath's clock gains large popularity for its ability to predict age across multiple tissues.

Although the epigenetic clock was initially developed for age prediction, the discovery of its connection with lifespan has made it a hallmark of biological age with an accelerated tick of the clock indicating a faster degeneration speed (15). Meanwhile, the concept of epigenetic age acceleration is proposed as the difference between DNAm age and chronological age (16). Positive epigenetic age acceleration (i.e., epigenetic age greater than chronological age) indicates that the tissue ages faster than would be expected, and has been linked with multiple age-related conditions such as obesity (17), frailty (18), osteoarthritis (19), cognitive decline (20), Alzheimer's disease (21), Parkinson's Disease (22) and all-cause mortality (23).

DNA methylation can be regulated by nutrients. Many B-vitamins are directly linked with DNA methylation by serving as substrates or cofactors in relevant pathways. With folate as the main substrate and related B-vitamins (e.g., vitamin B-2, vitamin B-6 and vitamin B-12) as cofactors, one-carbon metabolism plays a critical role in generating methyl groups that are later used for DNA methylation. Other nutrients such as choline and betaine are involved in the methionine cycle for the regeneration of methionine, a precursor for the universal methyl donor S-adenosylmethionine (SAM) (24). Multiple cohort studies have shown increased DNA methylation associated with higher intakes or blood levels of folate, vitamin B-2 and vitamin B-6 (25–27). Some bioactive food components, such as green tea polyphenols and soybean genistein, have inhibitory effect on DNMTs and can reduce cancer activities by reversing hypermethylation status of key tumour suppression genes (28). Besides DNA methylation pathways, a study of Yin et al. have found that vitamin C can promote DNA demethylation by enhancing activities of TET enzymes (29).

The close connection between nutrients and DNA methylation makes epigenetic clocks as ideal indices in ageing-related nutrition studies. Firstly, the emerge of epigenetic clocks provides an additional insight to verify the importance of diet in health management. The study of Quach et al. found that lower epigenetic age acceleration was associated with higher fish and poultry intake, moderate alcohol consumption and higher fruit and vegetable consumption, supporting the benefits of a plant-based diet with lean meats (30). Secondly, the epigenetic clock can be used to test DNA methylation-related hypothesis. Vitamin D deficiency has been associated with chronic pain, the leading cause of which is osteoarthritis (31). While underlying mechanisms of the association remain poorly understood, a possible explanation might be epigenetic alterations that have been related to both vitamin D (32) and osteoarthritis (19). The recent work of Strath et al. analysed the mediation effect of Horvath's epigenetic clock on the

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association between circulating vitamin D and pain status caused by knee osteoarthritis (33). Mediation analysis showed a complete mediation of the epigenetic clock, indicating that the chronic pain related to vitamin D deficiency was due to changes in epigenetic status (33). Last but not least, since alterations in DNA methylation precede phenotypic changes, the epigenetic clock can be a sensitive metric to evaluate nutrition treatment in ageing studies. Sae-Lee et al. studied the epigenetic changes in older adults (aged 65-75 years) with daily folic acid (400 μg/d) and vitamin B12 (500 μg/d) supplementation over a period of 2 years and found reduced Horvath's epigenetic clock in women with the MTHFR 677CC genotype (34), indicating that folic acid and vitamin B12 supplementation were effective in slowing down epigenetic age while such effect was genotype dependent.

In conclusion, nutritional epigenetics has highlighted the importance of diet for health management in ageing. Although the idea of using dietary intervention to combat ageing is compelling, issues such as food combinations, optimal doses and exposure time are needed to be addressed. The impact of sex and genotypes on nutritional epigenetics will also be an interesting point to look into for personalised dietary prescription that can leverage epigenetic effects. While more studies are still needed to answer those questions, the epigenetic clock can be a powerful index in the exploration.

Conflict of interest: The author declares no conflicts of interest.

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