DNA methylation states in supercentenarians

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Molecular mechanisms contributing to healthy ageing and longevity are not yet completely understood.[1] One potential mechanism involved is DNA methylation,[1] a process that serves as a dynamic regulator of cell function and can also be a means to define epigenetic age, an indicator of biological age.[1,2] Studying the epigenetic patterns of supercentenarians has special relevance in longevity research because epigenetics is the connection between the environment and the inherited genome.[1]

In the first part of the study by Shohei Komaki and colleagues,[3] published in *The Lancet Healthy Longevity*, the authors explored epigenetic signatures of exceptional longevity in Japanese centenarians and supercentenarians (ie, individuals aged 100–115 years). To identify the signatures, the analysis strategy included classification of the age-associated DNA methylation sites (CpG sites) into clusters on the basis of the concordance between non-centenarians (individuals aged 20–80 years) and centenarians (those aged 100 years or older). Specifically, using targeted bisulfite sequencing data, the authors first identified age-related trends of DNA methylation patterns in non-centenarians and then explored how the epigenetic signature of centenarians deviated from this trend. This creative approach might be a good choice for future studies. The functional roles of the epigenetic signatures were assessed using gene–protein pathway and network analyses, and the results suggest that potential biomolecular explanations, such as anti-inflammatory TGF-β signalling, underlie healthy ageing. Additionally, in the second part of the study, using the same sequencing data, the authors created an epigenetic clock based on calendar-age-associated DNA methylation level changes (ie, the first-generation epigenetic clock). They showed that centenarians clearly had lower epigenetic ages compared with their calendar ages. Data properties limited the analyses on the next-generation clocks in this study.

A DNA methylation profile of a whole-blood sample is an average profile of the different blood cell subtypes in the sample. Thus, this work might be followed up by studying some key questions, such as: are the epigenetic signatures of exceptional longevity similar in different tissues, separated cell subtype populations, or single cells? This information is relevant for a better understanding of the topic, as the current analysis was performed on whole-blood samples. Furthermore, as can be seen in, for example, PubMed search engine outputs with search words such as "Illumina methylation" and "targeted bisulphite sequencing", the methylation sites in targeted bisulfite sequencing data are not studied as widely as microarray-based DNA methylation data, and the overlap between the methylation sites covered by these two measurement types can be small, as shown in the study by Komaki and colleagues.[3] Further studies are needed to explore how methylation patterns in those genomic regions, which have not been so intensively studied before (eg, locations that can be covered using only sequencing-based methodologies), relate to lifestyle, ageing phenotypes, and mortality in different adult ages, and how heritable their methylation levels are.

I declare no competing interests.

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