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CRITICAL TOOLS

DNA methylation-based biomarkers and the epigenetic clock theory of ageing

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Abstract

Biomarkers and validating molecular targets of interventions that extend the human health span (HHS) have been difficult to develop. A recent clinical definition of ageing is the scientific representation of the fundamental mechanisms of ageing to serve as their indicators, but a mechanistic understanding of ageing has been lacking. Epigenetic clocks are molecular-based accurate age estimators for any tissue across the entire life course. These 'epigenetic clocks' link developmental and maintenance processes to biological ageing. Here, we provide a theory of life course. Epigenetic biomarkers may help to address long-standing questions in many fields, including the central question: why do we age?

Introduction

Since the 1990s, it has been recognized that valid and reliable biomarkers of ageing will be needed to achieve the ancient goal of understanding, slowing, halting or even reversing ageing[1–3]. Instead of using chronological age, which is the primary surrogate measure of the ageing process, Baker and Sprott proposed the identification of biomarkers that can predict the rate of ageing and the remaining life span of individuals[4]. According to them, changes with age[5–7] — in other words, to identify markers of biological age. In 1994, the US National Institute on Ageing initiated a programme with the expressed goal of identifying age-associated biomarkers to investigate and measure the ageing process[8]. The idea was that biomarkers of ageing would become especially considerable as medical as well as public health interventions that target ageing mechanisms become available[9]. Project_advocacy for biomarkers of ageing[10] and developed definitions of particular postulated cognitive models[11]. The latter, which was especially important, was a shift in scientific culture from the view of ageing as a consequence of random damage to the view that longer DNA methylation data sets to study associations between DNA methylation and ageing[12–14]. Although these studies were not designed to develop an accurate multi-tissue biomarker of ageing, they provided the first indication that DNA methylation data can be used

DNA methylation fluxed DNAm age is a continuous statistic of molecular processes that play a role in development, tissue maintenance and, ultimately, decline. DNAm age has been so-named because it is a measure of DNA methylation that is fluxed with age. Tissue function declines with age and is the developmental process and the maintenance of a minimum cell density for maintenance across a tissue (Fig. 1). The precise mechanisms linking the meta-molecular processes to the decline in tissue function are unknown, but may include changes in cell composition, cell senescence, stem cell exhaustion, and/or the loss of cellular identity. Independently, senescent cells, which are not pictured in Fig. 1, may contribute to tissue dysfunction and aging. Senescent cells have an altered secretory profile and are known to contribute to inflammaging. Inflammaging is a common contributor to many common diseases and is associated with increased mortality risk.

Full size image

Box 4 Effects of screen-on age acceleration

Show more

Anti-aging interventions

The great promise of DNAm age biomarkers of aging is the identification and/or validation of anti-aging interventions. Although the field of DNA methylation biomarkers of aging is nascent, a handful of studies already address this challenge in apparently fruitful ways that a healthy diet (high vegetable and fish intake), avoidance of obesity and physical activity are associated with slower intrinsic epigenetic age acceleration in blood[107,108]. These encouraging results are remarkable in that they were obtained using cross-sectional data[107,108]. Thus, they may reflect the effects of a healthy diet and physical activity rather than lifestyle changes that, in fact, slow biological aging. Longitudinal studies are needed to test whether only a small effect on epigenetic aging rates[109] or, for example, within a 12-week follow-up period, the substantial weight loss resulting from bariatric surgery can not only reverse but actually rejuvenate epigenetic age of human liver tissue samples[110]. Moreover, it is likely that anti-aging interventions will have tissue-specific effects. For example, glucocorticoid treatment of rheumatoid arthritis is associated with epigenetic age acceleration in buccal epithelial cells but not in blood cells[111].

To date, the most effective in vivo intervention against epigenetic aging are heterochronic transplantation experiments in mice. Specifically, young blood can rejuvenate old brain cells, thereby completely resetting the epigenetic clock[112]. In vivo, haematopoietic stem cell therapy resets the epigenetic age of blood of the recipient to that of the donor[113,114]. The dynamics of this process reveal a striking and short-term anti-aging phenomenon[113]. For example, a 6 months after a 50-year-old individual receives blood from a 20-year-old donor, the epigenetic age of the recipient's blood is 20 years old. However, this dramatic additional rejuvenation effect of 5 years disappears within the next 6 months, at which point the age of blood in the recipient becomes about 25 years old. Five years after transplantation, the blood of the recipient will have a DNAm age of 30 years—a genuine gain versus those donor droughts, which are subsequently regained[113].

Others have hypothesized that epithelial stem cell therapy may be an effective treatment for advanced prostate cancer. For example, it is hard to imagine that an epigenetic age measurement would be anything but elevated in a prostate cancer patient. Indeed, epigenetic age acceleration is a hallmark of prostate cancer[115]. Perhaps DNAm age measurements may be useful to monitor the success of stem cell therapy in this context. Specifically, a successful therapy would be one that not only reduces tumor burden but also reduces DNAm age. Likewise

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Ethics declarations

Competing interests

The Regents of the University of California is the sole owner of several patent applications directed at the invention of measures of epigenetic age estimation for which S.H. is a named inventor. K.R. declares no competing interests.

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Supplementary information

Glossary

Chronological age
The calendar time that has passed since birth. Zero is the time at birth. Negative numbers indicate prenatal ages, whereas positive numbers indicate postnatal ages.

Biological age
Also known as physiological age. organismal age or phenotypic age. This ambiguous concept is held to be dependent on the biological state of the individual.

Epigenetic age
The age estimate in years resulting from a mathematical algorithm based on the methylation state of specific CpGs in the genome. Negative numbers indicate prenatal ages.

CpG dinucleotides
Regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide in the linear sequence of bases along its 5′ to 3′ direction. Cytosines in CpG dinucleotides can be methylated to form 5-methylcytosine.

Epigenetic age estimators
Mathematical algorithms that use values assigned to the methylation state of specific CpGs in the genome to estimate the age of a person or biological sample. A multi-tissue age estimator allows one to estimate the age of any nucleated cell, tissue or organ.

Quasi-programme theories of ageing
Several variations of a theory that posits that ageing is not the intended outcome of biological processes but that some programmed processes nevertheless result in ageing. Therefore, the process of ageing can be viewed as quasi-programmed.

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