

Biological age from a pathological perspective

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Abstract

Biological age has the potential of providing a glimpse of the health of older people, as it may be less or more than chronological age. Assessment of DNA methylation has been shown to correlate with increasing age, but the correlation with aging phenotypes is still being studied. Therefore, knowing how a person responds to aging on a pathological basis would be a logical and justifiable approach to gaining more insight into what biological age means. An age-related lesion grading system called geropathology has been developed for animal models that can be quantitatively correlated with chronological age to provide translational information for human studies. However, geropathology platforms are not yet appreciated as impactful areas of aging research so more research funding is needed to move this concept forward.

Keywords: Biological age, geropathology, age-related lesion, chronological age

Biological age is a term used to designate how biologically younger or older a person is compared to their chronological age. It is somewhat imperfect since there is no current universally accepted way to determine biological age at the organismal level. Biological age would provide a highly informative insight into the health needs of older people. For example, a person with a chronological age of 63 might have a biological age of 44 and may not need any type of aging intervention, while a person with the same chronological age but with a biological age of 81 may need some type of aging intervention. This of course is a hypothetical example, but conceptually points out the high clinical relevance such an approach would have.

DNA methylation is one of the assessments currently receiving considerable attention [1]. It is based on the detection of DNA methylation of cytosines at CpG dinucleotides and has been shown to increase with increasing age in a variety of mammalian species including humans. The problem is there is still not enough information on how DNA methylation links to aging phenotypes.

In this regard, knowing how a person responds to aging on a pathological basis would be a rational and logical approach to gaining more insight into what biological age means. Assessing the pathological response to aging

quantitatively would be an ideal concept. If one considers all age-related lesions as important to assess, and not just those lesions associated with morbid disease, then a quantitative approach can be undertaken. Studies have already been reported in aging laboratory mice [2]. Mice are one of the most used species for research on aging and age-related diseases, and an age-related lesion grading system called geropathology has been generated and validated [3]. Geropathology platforms are currently being developed for other species including laboratory rats, pet cats, common marmosets, and rhesus macaques. Autopsies can routinely be conducted in these species providing tissues on a cross-sectional basis so average age-related lesion scores from a cohort can be statistically calculated for a specific organ. Average lesion scores from all major organs can then be used to obtain a pathological view of organismal aging. Of equal interest is the ability to calculate the biological age of individual organs because some organs will age at a different rate than others.

The geropathology platform works well in animal models where tissues can routinely be collected at autopsy. However, autopsies in older people that die are not routinely done, so how is geropathology relatable to human aging? The answer to this question is that the geropathology platform developed in mammals, from mice to nonhuman primates, can be used to test for translational markers that associate with age-related lesions in a particular organ. For example, preliminary unpublished observations in mice show that an increase in the urine albumin to creatinine ratio is associated with increased severity of age-related lesions in the kidney. Additional translational tissue samples that are being used to determine correlations with age-related lesions in multiple organs include blood

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and skin biopsies.

This brings up the question, then, of whether current assessments of biological age, such as DNA methylation, can be shown to link with geropathology platforms. Work in this area in animal models is just now being considered, but it is a concept that has not been a top priority in aging research. The impact on aging is not yet appreciated so research grants are not given appropriate scores by review committees, and few studies are being funded to move this vitally impactful area of aging research forward.

Declarations

Conflicts of interest: Warren Ladiges is a member of the Editorial Board of *Aging Pathobiology and Therapeutics*. All authors declare no conflict of interest and were not involved in the journal's review or decisions related to this manuscript.

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