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# News & views

Ageing

# Gene expression reveals mortality risk and age

João Pedro de Magalhães

Massive analyses of RNA transcripts from rodents, monkeys and humans reveal hallmarks of ageing that could expedite the development of anti-ageing interventions.

How quickly is a person ageing, and what is their risk of dying in the near future? Can lifespan be predicted from molecular data? These fundamental questions in ageing research have implications for drug discovery, clinical trials and precision medicine. The ability to estimate age, mortality risk and lifespan in model organisms such as rodents, is important because it can speed up the testing of interventions that aim to extend healthspan and lifespan. Writing in *Nature*, Tyshkovskiy *et al.*[1] report a computational model for estimating age and predicting mortality using large-scale gene-expression (that is, transcriptomic) signatures that are common across several tissues and four mammalian species.

Chronological age represents the time passed since an individual was born, yet people with the same chronological age can differ in their health, functional capacity and life expectancy. Identifying biomarkers to estimate those differences has long been a goal for longevity researchers. Over the past 15 years, they have achieved a major breakthrough: the development of 'epigenetic clocks' based on patterns of chemical modifications to DNA, namely the addition of methyl groups (methylation).

Epigenetic clocks can estimate chronological age, mortality risk (the likelihood of death) and life expectancy (how long an organism is expected to live) from blood samples with remarkable accuracy[2]. The multi-tissue Horvath clock, for example, can estimate age on the basis of methylation at 353 genomic sites, with a median error of only 3.6 years[3]. 'Pan-mammalian' clocks have been developed that can estimate age across different species and tissues[4]. Deviations between the methylation age and chronological age of tissues are associated with the risk of various diseases[2]. One drawback of epigenetic clocks, however, is their limited interpretability, given that the mechanisms that underpin age-related methylation changes are still debated.

Changes in gene expression underlie normal biological processes and are extensive in many diseases. Genome-wide studies[5,6] of age-related gene-expression changes have identified molecular signatures that are common to a range of tissues and species. These signatures are linked to alterations in inflammation, the function of mitochondria (the organelles that generate cellular energy) and how the meshwork of molecules that surrounds cells (the extracellular matrix) is organized[5]. Because the signatures reflect changes in the activity of specific genes, transcriptomic biomarkers are more interpretable than are epigenetic ones. However, the accuracy and applicability of transcriptomic biomarkers have been more limited, perhaps because gene expression is more dynamic than is DNA methylation.

Tyshkovskiy *et al.* developed transcriptomic clocks that have similar accuracy to epigenetic clocks, and that can be applied across tissues and species. Because mortality risk increases with age, and many processes unrelated to ageing influence health, developing and

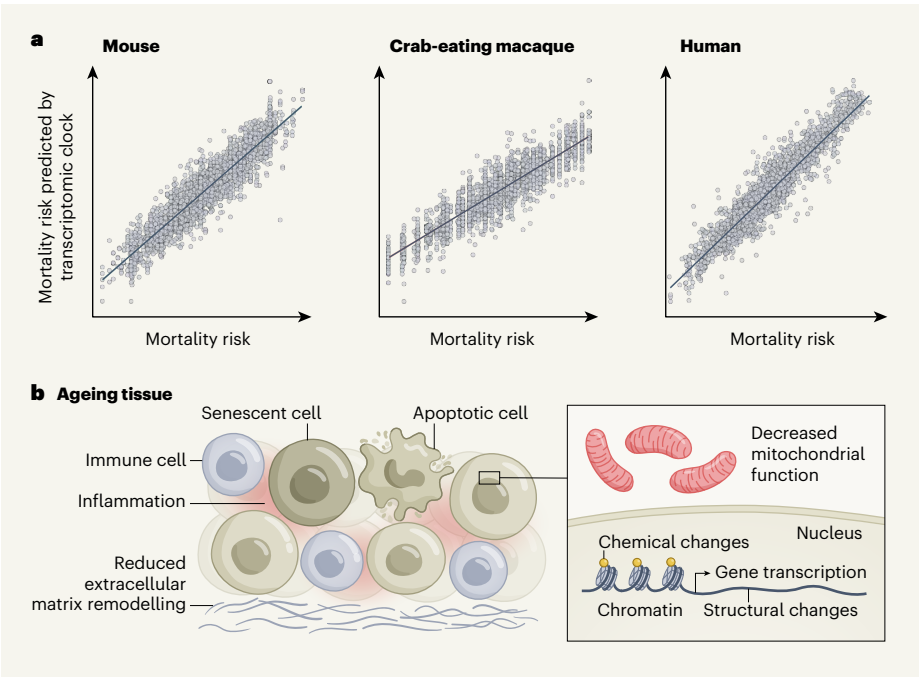


**Figure 1 | A biological marker of ageing in mammals.** **a**, Tyshkovskiy *et al.* integrated thousands of gene-expression (transcriptomic) data sets to identify transcriptomic signatures of ageing that are common to different mammalian species and tissues. They created a computational model known as a 'transcriptomic clock', which accurately estimates chronological age, mortality risk (the likelihood of death) and lifespan (how long an organism is expected to live) on the basis of these signatures. The graphs show the strong correlation between actual expected mortality risk and that predicted by the transcriptomic clock for mice, crab-eating macaques (*Macaca fascicularis*) and humans. (Adapted from Fig. 2a of ref. 1.) **b**, The biological pathways that the transcriptomic ageing signatures are linked to include upregulation of inflammation and immune activation; downregulation of metabolism and the function of mitochondria (which generate cellular energy); alterations in the cell cycle, including cell death (such as apoptosis) and cellular senescence (in which proliferative cells stop dividing); changes in chromatin modifications (structural and chemical changes to packaged DNA) and gene transcription; and reduced remodelling of the extracellular matrix (a meshwork of molecules that surrounds cells and maintains tissue health).

validating anti-ageing interventions should rely on assessing whether a given intervention affects mortality and lifespan. Transcriptomic clocks could prove to be valuable readouts of that assessment. Genetic, lifestyle and pharmacological interventions could be evaluated on the basis of their effects on mortality-associated gene expression, potentially enabling shorter preclinical and clinical trials in rodents and humans.

To develop their clocks, Tyshkovskiy *et al.* used mice from the Interventions Testing Program (ITP), run by the National Institute on Aging, a part of the US National Institutes of Health. This programme is arguably the most comprehensive effort to test longevity interventions in mammals. The authors sequenced the transcriptomes (that is, all RNA transcripts) of mice treated with 20 pharmacological interventions, and they integrated these data with transcriptomic data sets from 3,824 mouse samples, 663 rat samples, 2,623 samples from a non-human primate (crab-eating macaque, *Macaca fascicularis*) and 4,003 human samples. This enabled the authors to develop rodent-specific multi-tissue clocks for age, mortality risk and lifespan, as well as multi-species clocks for age and mortality risk (Fig. 1a).

The authors validated their clocks using statistical approaches and independent data sets, including those from rodent models of accelerated ageing and of specific conditions, such as Alzheimer's disease and chronic kidney disease, and from cellular models of ageing and rejuvenation. Notably, applying the clocks to single-cell data from normal mice of different ages revealed that more than 90% of cell types exhibited increased transcriptomic age, suggesting that ageing occurs at the cellular level.

Analysing the networks of co-expressed genes that comprise the clocks, the authors identified key biological pathways, including inflammation and immune responses, mitochondrial function, epigenetic regulation and extracellular-matrix organization (Fig. 1b) — processes that have repeatedly been associated with ageing[5,6]. Furthermore, a protein called p21, which is a marker of cellular senescence (in which proliferative cells stop dividing), was found to be overexpressed with age and associated with mortality risk. Tissues from people with various diseases exhibited an acceleration in transcriptomic age. Inflammation emerged as a common feature of these diseases, consistent with its well-established association with several age-related conditions[7]. All of these processes can be considered transcriptomic hallmarks of ageing because they are observed across tissues and species. Compared with epigenetic clocks, transcriptomic hallmarks of ageing could help researchers to pinpoint which processes are modulated by interventions or diseases.

Although these transcriptomic hallmarks suggest that there are coordinated, system-level features of ageing, a key open question concerns their mechanistic relevance. The observed patterns of gene expression are mostly correlative, and it is unclear whether these clocks capture biological ageing itself or reflect processes that correlate with age. Indeed, the expression levels of genes that protect against and respond to cellular stress have long been known to increase with age, which is suggestive of adaptive responses, rather than causal drivers. It is therefore uncertain whether transcriptomic signatures drive ageing, result from it or represent compensatory mechanisms. Similarly, it is unclear how different transcriptomic ageing processes influence each other and whether manipulating certain processes to return them to a youthful state would slow ageing overall.

This study also highlights the importance of large data sets in ageing research. Computational models are only as good as the data on which they are trained. Although abundant data exist for estimating chronological age, data on interventions that strongly extend lifespan are limited. Even in rodents, longevity effects are often modest: the compound rapamycin, which is the ITP's most effective longevity intervention, extends median lifespan by roughly 25% (ref. 8). In humans, the absence of established longevity interventions complicates the interpretation of new biomarkers. If, in the future, a biomarker fails to indicate that an intervention had an effect, it would be unclear whether this reflects a limitation of the intervention or of the biomarker itself.

Finally, the growing number of ageing biomarkers and clocks, which often produce differing results, is concerning. It could lead to the selective reporting of study outcomes, impede accurate interpretation and make studies harder to reproduce. Researchers must therefore select appropriate biomarkers for specific applications and resist the temptation to select measures that support their hypotheses — highlighting the need for any ageing biomarker to be validated carefully.

**João Pedro de Magalhães** is in the Department of Inflammation and Ageing, College of Medicine and Health, University of Birmingham, B15 2WB, UK.
e-mail: jp@senescence.info

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