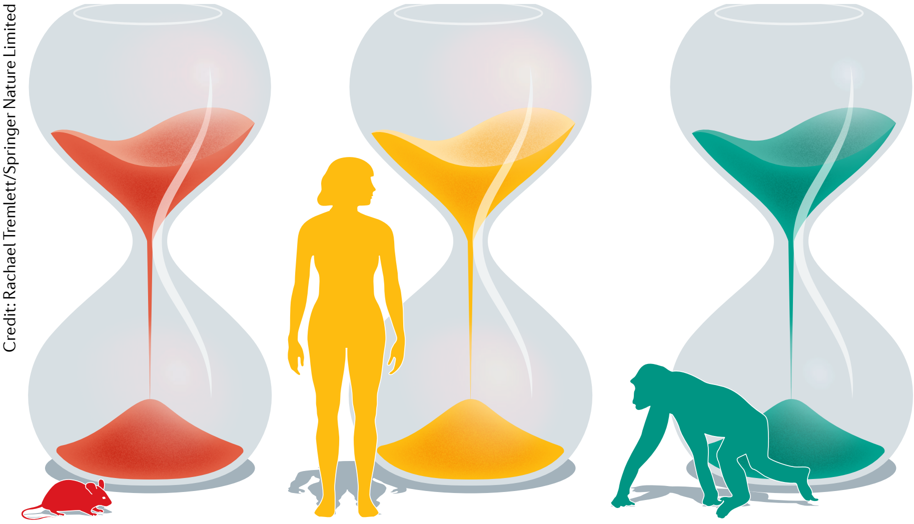

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AGEING

Research in metabolic ageing — a tale of mice versus humans?

Susanna M. Hofmann and Rüdiger Landgraf

The investigation of age-induced disease progression in humans is time consuming and resource intensive. One burning question for the exploration of human metabolic ageing is how similar metabolic changes over a lifetime are between humans and mice. A recent study highlights similarities and disparities between these species throughout their lifespan.

Refers to Palliyaguru, D. L. et al. Fasting blood glucose as a predictor of mortality: lost in translation. *Cell Metab.* https://doi.org/10.1016/j.cmet.2021.08.013 (2021).

Ageing is characterized by functional and metabolic decline and is considered a key contributor to the development and/or exacerbation of numerous noncommunicable diseases. As preclinical research breakthroughs in healthspan and lifespan are becoming more frequent, there is greater demand for reliable and practical markers for the assessment of an individual's biological age and morbidity and/or mortality risks. At present, obesity and its associated metabolic dysfunctions are the major cause of many chronic, debilitating and life-shortening diseases, such as type 2 diabetes mellitus, atherosclerotic cardiovascular disease and renal disease, as well as certain carcinomas, chronic obstructive pulmonary diseases and neurodegenerative disorders.

Classic risk factors for metabolic diseases, such as hyperglycaemia, hyperinsulinaemia, dyslipidaemia, arterial hypertension and inflammatory profiles, are routinely used to assess patients with obesity. However, a population-based prospective cohort study of roughly 400,000 participants published earlier this year showed that people with obesity are a heterogeneous group. Additionally, this study found that the risk of adverse clinical outcomes (such as heart failure, respiratory disease, atherosclerotic cardiovascular disease and type 2 diabetes mellitus) is increased in people with obesity even if they have a normal metabolic profile[1]. This current lack of accurate and reliable disease predictors to correctly stratify individuals with intermediate hyperglycaemia (prediabetes) according to risk was highlighted in a paper published in early 2021. This study showed that multivariable subphenotyping using variables derived from oral glucose tolerance tests, MRI-measured body adipose distribution, liver fat content and genetic risk calculations could reflect key pathological features that potentially underlie different outcomes of organ complications[2]. It is becoming increasingly evident that more basic research is required to develop and validate such diagnostic approaches for the prevention and treatment of many chronic debilitating diseases.

The exploration of disease progression and ageing in humans is time and resource intensive. For these reasons, the laboratory mouse has become the model organism of choice in preclinical research. Mice have several scientific and practical advantages as a model organism. Firstly, powerful experimental approaches to modify gene function and to evaluate molecular, cellular, tissue or systems biology are readily available for mice. In addition, mice thrive in laboratory environments, have a short lifespan and can be housed economically. These circumstances, together with the sequencing of the mouse genome, have enabled scientists to use mice to study the biological functions and pathological roles of genes implicated in metabolic regulation. Although it has been widely accepted that most basic metabolic and physiological mechanisms are conserved between species, there are several barriers to the use of mice for understanding and developing therapies for human metabolic diseases. For example, monogenic mouse models develop obesity and diabetes mellitus at accelerated rates that do not reflect the slower changes in humans. Additionally, mice are commonly housed below their thermoneutrality, while humans spend most of their time at temperatures close to thermoneutrality. Another major problem is the poor reproducibility of preclinical mouse studies in oncology, cardiovascular biology and metabolism[3], which raises the issue of whether findings obtained in mice are relevant to human pathophysiology.

The question of how similar metabolic changes over a lifetime are between humans and mice is particularly important for the exploration of human metabolic ageing. Even though mice are widely used to investigate human ageing, evidence regarding the physiological mouse ageing process is scarce. In addition, there exist few comparative studies on the differences in the ageing process between mouse strains. This lack of comprehensive analysis of normal mouse ageing across sex and strains has, up to now, prevented the use of mice as reliable models for human ageing. As a consequence, researchers have not yet identified translationally relevant preclinical biomarkers, which are required

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for the development of successful anti-ageing treatments[4].

To address this gap, Palliyaguru and colleagues analysed phenotypic and biological predictors of normal mouse ageing and examined functional and biomolecular variability in inbred and genetically heterogeneous ageing mouse populations. The ultimate aim of this study was to provide a platform for evaluating interventions that might delay the progression of phenotypic and biological ageing in humans (Study of Longitudinal Aging in Mice (SLAM))[5]. Using this platform, Palliyaguru et al. compared the longitudinal trajectories of three well-established human biomarkers of metabolic health (fasting blood levels of glucose, body weight and body adiposity) between humans, mice and non-human primates[6]. In addition, they examined the associated mortality risks of each of these three biomarkers. For that purpose, the authors validated the data generated by SLAM across the lifespan of 1,241 mice against observations in the ongoing Baltimore Longitudinal Study of Aging (BLSA; 3,023 individuals), one of the world's oldest studies on healthy, normative ageing in humans. The data from these two studies were also compared with data from studies of non-human primate ageing at the National Institute on Aging and the Wisconsin National Primate Research Center (a total of 254 non-human primates).

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To account for the large variation in life expectancy across species, the authors first determined a common time variable to allow comparable measurements of rates of change between the three species. They chose 5% of the median life expectancy (6 weeks for mice, 1 year for non-human primates and 4 years for humans). This choice allowed them to model rates of change in a linear fashion, which facilitated their interpretation of the data. The authors detected similar trajectories for two of their endpoints, body weight and adipose tissue, in all three species. This finding validated mice and non-human primates as models for preclinical ageing research for these two parameters. By contrast, their analysis revealed that age-associated fasting blood levels of glucose trajectories differ substantially between mice and non-human primates and between mice and humans. Glucose levels in mice remained stable until mid to late life and thereafter decreased at a statistically significant rate of −3.08% every 6 weeks. By contrast, in non-human primates and humans, glucose levels increased throughout life at the statistically significant rates of 0.48% per year and 0.70% per 4 years, respectively.

Palliyaguru and collagues even identified an inverse correlation between glucose levels and survival rates for mice versus non-human primates or humans that has been reproduced in two independent studies[7,8]. The authors also observed reduced and delayed peaks of metabolic measurements in female individuals of the three species, potentially indicating a survival advantage that needs to be explored further[6]. The marked sex differences in all three species in terms of absolute values, age at which indices peaked and mortality risks highlight once again the importance of generating sex-specific data to identify novel valid personalized drug targets against age-induced metabolic diseases.

The results obtained by Palliyaguru and colleagues highlight pitfalls and limitations of mouse models for research into human pathology induced by metabolic ageing, and at the same time confirm their value for metabolic studies. There is little doubt that mice can still serve as a useful model in early stages of the discovery process of human metabolic ageing. In particular, studies in mice remain important for assessing functional genomics, drug targeting and in vivo validation of test compounds and their toxicology[9]. It is important, however, to be aware of the limitations of mouse models and to avoid using them for scientific hypotheses they are unsuitable to address. We must, therefore, carefully determine under which conditions mouse models can provide relevant insight before we begin a metabolic ageing research project.

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https://doi.org/10.1038/s41574-021-00597-9

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Competing interests

The authors declare no competing interests.