Mouse epigenetic aging clock uncovered

April 12 2017

Credit: Martha Sexton/public domain

Ageing in humans (and animals) can be seen as either an inevitable process of wear and tear or as an inherent biological programme by which the lifespan of each species is more or less predetermined. Recent research has shown that DNA methylation, an epigenetic modification which alters how DNA is read and expressed without altering the underlying sequence, can show age-related changes.

A sub-set of these modifications are so accurate that chronological age in humans can be predicted +/- 3.6 years from any tissue or fluid in the body (Horvath S. 2013). This is by far the best biomarker of age

available and is referred to as the epigenetic clock. Interestingly, analysis of DNA methylation can also provide information on biological age, which is a measure of how well your body functions compared to your chronological age. For instance, people suffering from fatty liver disease have a faster ticking clock, while centenarians have a slower clock.

But, how does this epigenetic clock work? And is it possible to change the ticking rate? Researchers at the Babraham Institute and the European Bioinformatics Institute have now identified a mouse epigenetic ageing clock. This work, published today in *Genome Biology*, shows that changes in DNA methylation at 329 sites in the genome are predictive of age in the mouse with an accuracy of +/- 3.3 weeks. Considering that humans live to approximately 85 years and mice to 3 years, the accuracy of the mouse and human clocks (better than 5%) are surprisingly similar.

Using the mouse model, researchers also showed that lifestyle interventions known to shorten lifespan sped up the clock. For example, removing the ovaries in female mice accelerates the clock, something that is also observed in early menopause in women. And interestingly a high fat diet which we know is detrimental to human health also accelerates the ageing clock. Remarkably, researchers were able to detect changes to the epigenetic clock as early as 9 weeks of age, bearing in mind that the lifespan of a mouse can easily be more than 3 years, this represents a massive reduction in both time and cost which the researchers believe will accelerate future ageing discoveries.

Tom Stubbs, PhD Student in the Reik group at the Babraham Institute and lead author of the paper, said: "The identification of a human epigenetic ageing clock has been a major breakthrough in the ageing field. However, with this finding came a number of questions about its conservation, its mechanism and its function. Our discovery of a mouse epigenetic ageing clock is exciting because it suggests that this epigenetic clock may be a fundamental and conserved feature of

mammalian ageing. Importantly, we have shown that we can detect changes to the ticking rate in response to changes, such as diet, therefore in the future we will be able to determine the mechanism and function of this epigenetic clock and use it to improve human health."

Dr. Marc Jan Bonder, postdoctoral researcher at the European Bioinformatics Institute, adds: "Dissecting the mechanism of this mouse epigenetic ageing clock will yield valuable insights into the ageing process and how it can be manipulated in a human setting to improve health span."

With further study, scientists will be able to understand the inner mechanistic workings of such a clock (for example using knowledge about enzymes that regulate DNA methylation in the genome) and change its ticking rate in the mouse model. This will reveal whether the clock is causally involved in ageing, or whether it is a read-out of other underlying physiological processes. These studies will also suggest approaches to wind the ageing clock back in order to rejuvenate tissues or even a whole organism.

Professor Wolf Reik, Head of the Epigenetics Programme at the Babraham Institute, said: "It is fascinating to imagine how such a clock could be built from molecular components we know a lot about (the DNA methylation machinery). We can then make subtle changes in these components and see if our mice live shorter, or more interestingly, longer." Such studies may provide deeper mechanistic insights into the ageing process and whether lifespan in a species is in some way programmed".

More information: Thomas M. Stubbs et al, Multi-tissue DNA methylation age predictor in mouse, *Genome Biology* (2017). DOI: 10.1186/s13059-017-1203-5

Provided by Babraham Institute