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PERSPECTIVES

EPIGENETICS

A mammalian DNA methylation landscape

A study of 348 species offers clues into the diversity of mammalian life spans

By **Alex de Mendoza**

Mammals vary greatly in life span; for example, the bowhead whale (*Balaena mysticetus*) can live up to 200 years, whereas giant Sunda rats (*Sundamys muelleri*) only live for about 6 months in the wild. This disparity is encoded in the genomes of each species; however, which genes are linked to these traits is still poorly understood. Because mammals have approximately the same genes, variation in how these genes are regulated should be important in determining the timing of aging. On page 647 of this issue, Haghani *et al.* (*1*) describe a large-scale study of DNA methylation (which has a role in gene regulation) in a diverse range of mammalian species. They identified genomic regions that might govern life-span variation among lineages, which could help uncover the molecular drivers of life span and other traits in mammals.

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DNA methylation is a small chemical modification that occurs in most cytosines that are followed by a guanine (CpGs) in mammalian genomes. DNA methylation information is inherited after mitosis; however, it is not static during development or among tissues. DNA methylation differences occur mostly at "enhancers," stretches of DNA that dictate the expression of nearby genes. Thus, each cell type and tissue in the body has a precise DNA methylation signature, like a barcode. Although DNA methylation is frequently not the main factor that dictates gene regulation, it is a robust biomarker for gene activity and cell identity (*2*, *3*).

DNA methylation is easier to measure than other classic gene regulatory mechanisms, such as histone modifications or transcription factors. However, reliable quantification of DNA methylation across the genome is not trivial because current gold-standard methods such as whole-genome bisulfite sequencing require a reference genome and large amounts of data. This makes studying DNA methylation across a large number of samples difficult, but large sample sizes are required to find significant associations between DNA methylation and complex traits such as life span or weight (*4*). This limitation can be overcome by using microarrays to probe for specific subsets of CpGs. Such microarrays have previously been used for studies in humans and mice. Haghani *et al.* used a recently designed pan-mammalian DNA methylation microarray that captures a subset of the CpGs that are conserved across all mammals, including marsupials and egg-laying mammals (although with lower resolution for these two lineages), at high confidence and for a fraction of the cost of other methods (*5*). The microarray does not need a reference genome, and the CpGs are directly comparable across samples and species.

Haghani *et al.* profiled the DNA methylation of 15,456 samples from 348 species, including up to 70 tissues per species. They used the data from blood (a tissue comparable across species) to obtain species relationships solely on the basis of DNA methylation. This clustering largely recapitulated the mammalian tree of life, which indicates that phylogeny and species relatedness is a major factor that underlies variation in DNA methylation. Still, this "phylogenetic" signal did not explain all the variation.

To disentangle the variation in DNA methylation explained by phylogeny from that explained by other traits such as age or tissue of origin, the authors performed unsupervised clustering of all the CpGs (in all species and all tissues) according to their covariation. CpGs that gained or lost methylation in a coordinated manner across many samples were grouped together into modules. The authors then looked for associations between these modules and a range of features, including species traits such as taxonomy or life span and individual traits such as age, sex, or weight. As expected, many CpG modules had methylation patterns that were specific to a taxonomic group. However, other modules included groups of CpGs whose methylation status was enough to discriminate the organ or sex of the sample regardless of species.



DNA methylation was profiled in species including the African elephant (*Loxodonta africana*, left), which lives for 70 years on average, and the lab mouse (*Mus musculus*, above), which lives for an average of 2 years.

Several CpG modules were associated with life span. Variation in DNA methylation in these genomic regions explained, to some extent, the differences in life span across species. This finding is linked to the discovery that as humans and mice age, DNA methylation changes in many genomic regions (*6*). This has allowed the construction of so-called "epigenetic clocks," which are mathematical models that enable the prediction of biological age on the basis of methylation status of specific CpGs (*7*). Because the relative onset of aging could be a major factor in determining species maximum life span (*8*), identifying CpG modules that are linked to cross-species variation in life span might identify gene regulatory events that are responsible for differential aging processes in mammals.

Among the genomic regions that were associated with life-span variation, some were predicted to be regulated by transcription factors important for pluripotency. These pluripotency factors encode proteins, such as octamer-binding protein 4 (OCT4) or SRY-box transcription factor 2 (SOX2), whose expression can revert an adult differentiated cell to an embryonic-like cell. OCT4 and SOX2 belong to a group of transcription factors known as the Yamanaka factors, the experimental reactivation of which decreases markers of aging in mice (*9*, *10*). Haghani *et al.* found that experimental reexpression of the Yamanaka factors in adult mice affected the methylation status of some CpG modules associated with life-span variation. Therefore, regulation of these factors across the life of mammals might drive different life spans, with some species expressing them for longer.

The study of Haghani *et al.* shows that DNA methylation can be a powerful biomarker across mammals. The ability to rapidly measure methylation in any DNA sample and discriminate characteristics such as age, tissue, or sex may have multiple applications. For example, in conservation biology, it could help predict the age of individual animals that would be otherwise hard to assess in the field. Similarly, the epigenetic signature of exposure to pollutants and its effect on biological aging could now be assessed in wild animals (*11*).

The association between DNA methylation and life span is fascinating, although the molecular determinants of aging onset and how life span is encoded in the genome are still far from clear. Because the DNA methylation microarrays represent just a subset of the genome, further technological developments that provide full-resolution methylation maps across the genome might be able to identify species-specific adaptations in nonconserved genomic regions. Furthermore, because CpG methylation status is usually the consequence of complex upstream processes rather than the cause, precisely how these DNA methylation changes explain aging or life span is not yet clear. But now there is a robust high-throughput DNA-based marker to molecularly assess traits across mammals. Therefore, experimental treatments aimed at modifying aging, such as calorie-restricted diets or high-fat diets, can now be tested in nontraditional model species with distinct metabolic adaptations, and epigenetic aging can be measured. ■

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