DO EPIGENETIC CHANGES CAUSE AGING IN MAMMALS?

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Chromatin, the DNA-protein complex that stabilizes the genome and dictates gene expression, is one of the most difficult structure a cell has to maintain over a lifetime. Studies in budding yeast have pointed to changes in chromatin organization and gene expression as a main contributor to aging in that species, raising the possibility that similar processes underlie ageing in more complex organisms. In mammals, numerous epigenetic changes have been noted during aging, including DNA methylation and histone modification and gene expression changes. Changes in chromatin are also known to precede metabolic diseases, neurodegeneration, and cancer, and the underlying basis of cellular senescence undoubtedly has a chromatin component. However, the mechanism that drives these epigenetic changes and whether they contribute to aging is still debated. In mammals, evidence is accumulating that the relocation of chromatin factors in response to DNA damage is a major upstream cause of the gene expression changes that occur during aging (the “RCM” hypothesis). We have developed a novel model called the “ICE mouse” (for inducible changes in epigenetics) that allows us to induce a few DSBs in non-coding regions of the mouse genome within all tissues, then switch the system off and monitor the effects on tissues and age-related physiology. Consistent with the RCM hypothesis, ICE mice exhibit metabolic changes, decreased bone density, muscle and brain function, cataracts, skin aging, and frailty, among other effects consistent with aging. RNA-seq and ChIP-seq experiments indicate that lipid metabolism and inflammation pathways are involved and that chromatin is altered in specific ways. These experiments are consistent with epigenetic change driven by DNA repair processes as an upstream cause of aging in mammals. Further work will assess whether this process can be slowed or reversed using known and novel agents.