Do epigenetic changes cause aging in mammals?

Summary
Increasing evidence indicates that epigenetic changes are an upstream, cause of aging in eukaryotes. Studies in budding yeast were the first to point to changes in chromatin organization and gene expression as major contributors to aging. In mammals, numerous epigenetic changes have been noted during aging, including DNA methylation, histone modifications, and gene expression changes. The underlying basis of cellular senescence also has a chromatin component. However, the mechanism that drive 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 DNA cuts in non-coding regions of the mouse genome across 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 an early onset of 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 changes to the binding of FOXO1 and AP-1, two transcription factors involved in metabolic and stress responses, are an underlying cause of the epigenetic and gene expression changes seen during aging of ICE and wildtype mice. These experiments are consistent with epigenetic change driven by DNA repair 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 that reprogram cells to a more youthful epigenetic state.