H3K4me1 marks DNA regions hypomethylated during aging in human stem and differentiated cells

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In differentiated cells, aging is associated with hypermethylation of DNA regions enriched in repressive histone posttranslational modifications. However, the chromatin marks associated with changes in DNA methylation in adult stem cells during lifetime are still largely unknown. Here, DNA methylation profiling of mesenchymal stem cells (MSCs) obtained from individuals aged 2 to 92 yr identified 18,735 hypermethylated and 45,407 hypomethylated CpG sites associated with aging. As in differentiated cells, hypermethylated sequences were enriched in chromatin repressive marks. Most importantly, hypomethylated CpG sites were strongly enriched in the active chromatin mark H3K4me1 in stem and differentiated cells, suggesting this is a cell type-independent chromatin signature ofDNA hypomethylation during aging. Analysis of scedasticity showed that interindividual variability of DNA methylation increased during aging in MSCs and differentiated cells, providing a new avenue for the identification of DNA methylation changes over time. DNA methylation profiling of genetically identical individuals showed that both the tendency of DNA methylation changes and scedasticity depended on nongenetic as well as genetic factors. Our results indicate that the dynamics of DNA methylation during aging depend on a complex mixture of factors that include the DNA sequence, cell type, and chromatin context involved and that, depending on the locus, the changes can be modulated by genetic and/or external factors.