Genome Architecture Indicates Cellular Potential in Embryonic Stem Cell Differentiation

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The dynamic organization of the human genome is largely dependent on the nucleosome occupancy. Changes in nucleosome distribution allow access to the underlying DNA, and nucleosomes have been observed to transiently move along the genome as part of their role in gene expression. Important studies have mapped human nucleosome distributions genome-wide, but the role of chromatin structure in stem cell differentiation has not been addressed. I utilized an MNase-Transcription Start Site Sequence Capture method (mTSS-seq) to map the nucleosome distribution at human transcription start sites genome-wide in various h9 stem cell derivatives. Additionally, I compared sensitivity and occupancy of nucleosomes at certain time points throughout the cell line of differentiation to observe patterns between induced pluripotency and enrichment in genes. I demonstrated that nucleosome architecture and sensitivity is closely linked to cell-type specific physiology. I confirmed that nucleosome occupancy is increased in almost all 20,000 human genes recorded in the derivative cell lines. These altered nucleosome architectures are consistent between 8 out of 9 stem cell lineages indicating that the stem cell is becoming more restricted in terms of its functionality as it progresses down the differentiation pathway. I demonstrated that the nucleosome alterations are driven by the underlying DNA sequence and potentiate transcription factor binding. I concluded that DNA-directed nucleosome redistributions are widespread along the stem cell differentiation pathways. The results suggest a fundamental role for chromatin structure in cellular differentiation.

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