

Acetylation or methylation of lysines residues of histones, are among histones post-translational modifications causing chromatin conformational changes; which then regulate the recruitment of transcriptional factors and other chromatin binding proteins to DNA. Histone acetylation is modulated by two sets of enzymes HATs and HDACs, both involved in the regulation of gene transcriptional programs. Inhibition of HDACS promote cell proliferation and reprogramming. Class I, and II HDACs including class II HDAC Sirtuins play a role in limiting the reprogramming process induced by the transcription factors Nanog, Sox, Oct4; and HDAC inhibitors such as VPA or TSA significantly enhance differentiation by down-regulating pluripotency genes. Histone methylation marks of histone H3 are often involved in regulation of gene expression (H3K4me1), transcriptional elongation (H3K36me3) and gene silencing (H3K9me3, H3K27me3). In ESC, bi-valent domains are defined by the simultaneous presence of both H3K27me3 and H3K4me3 marks; genes which have only H3K27me3 or none of these marks are not involved in cell differentiation; and genes involved in cell differentiation present only H3K4me3 mark, and become active. In ESC and iPSC, H3, H4 acetylations; and H4K36me2, H3K4me3 levels are increased whereas heterochromatin is reduced which correlates to a more open chromatin organization important for pluripotency. Chromosomes in the nucleus, are organized in ~1Mb non-overlapping territories (CT) of open and closed chromatin domains. Pluripotency genes activation, such as Nano or Oct4, is correlated with gene positioning inside the nucleus. Chromatin decondensation and chromatin looping out of the CT increase this transcriptional activation and also, enable long-range regulatory gene interactions.

Nuclear domains act as barrier against the spreading of heterochromatin and partition chromatin into transcriptionally active and inactive chromatin regions. They include:

- **Replication domains:** large chromosome domains where replication timing is regulated. Upon differentiation of ESCs to NPCs, chromatin domains reorganize switching from early to late and late to early replication timing. Concentration of active histone marks is found at domain boundaries: making these domains part of the pluripotency signature.
- **Lamina-associated-domain (LADs) and LOCKS domains:** in differentiated cells, LOCKs overlap with LADs, and presence of inactive chromatin domains are important in silencing non-lineage-specific genes by facilitating their association with the nuclear lamina. Both types of domains are enriched in CTF binding sites. Contrary to LADs, LOCK distribution and abundance changes upon differentiation.
- **Topological domains:** are local chromatin interaction domains enriched with SINE elements, housekeeping and tRNA genes.

Upon cellular reprogramming, these nuclear domains revert to the undifferentiated state to the exception of early to late replicating domains.