Mechanisms of Heterochromatin Positioning in the Nucleus

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Spatial segregation of transcriptionally active euchromatin and silent heterochromatin is an important factor regulating nuclear functions. Majority of the eukaryotic nuclei have conventional architecture with transcriptionally active euchromatin residing in the nuclear interior and heterochromatin abutting the nuclear periphery and the nucleolus. Recently we found a unique exception from the above rule, nuclei of rod photoreceptor cells of nocturnal mammals. For optical reasons, heterochromatin is concentrated in the center of these nuclei whereas euchromatin lines the nuclear periphery, thereby forming an inverted nuclear organization in comparison to conventional nuclei. In both conventional and inverted nuclei, chromosomes acquire a complex folded structure which adapts to the shape of the nucleus and secures correct intranuclear positioning of eu- and heterochromatin regions.

To elucidate possible mechanisms of establishing of inverted *versus* conventional nuclear architecture, we carried out a detailed study of epigenetic landscape in both nuclear types. We showed that major epigenetic factors associated with eu- or heterochromatin remain similar in conventional and inverted nuclei. Moreover, depletion of methylation code writers (e.g., Suv3-9, Suv4-20, G9a) or readers (e.g., MECP2) does not affect global nuclear architecture in both cases.

Next we analyzed spatial arrangement of heterochromatin in tissues from wild type and mice with mutations in the lamin B receptor (Lbr) and lamin A/C (Lmna) genes. We identified two mechanisms tethering peripheral heterochromatin to the nuclear envelope, an LBR-dependent and lamin A/C-dependent, which are sequentially used at early and late stages of differentiation, respectively. Tethers have opposite effects on the expression of tissue-specific genes: selective disruption of lamin A/C downregulates whereas absence of LBR upregulates muscle gene expression. Importantly, the absence of both LBR and LA/C leads to loss of peripheral heterochromatin and inversion of nuclear architecture with heterochromatin localizing to the nuclear interior in non-rod cells.

Taken together, our data suggest that the major epigenetic factors do not play a crucial role in the choice between inverted and conventional nuclear architecture. Conventional mammalian nuclei relay on strong redundancy of epigenetic code itself and its writers, whereas the inversion in rods relies on absence of specific readers, LBR- and lamin A/C-dependent peripheral heterochromatin tethers.