Genome resilience safeguards functional chromatin states

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Résumé

Cellular identity is defined by the expression of specific gene sets. Once established, it is maintained through alternative chromatin states, which are propagated through cell divisions. Epigenetic systems, comprising DNA and histone modifications, and 3-dimensional chromatin organisation, can assign alternative activity states to the same DNA sequence. On the other hand, cellular memory is a collective term that refers to mechanisms that maintain these sustained cellular states in response to transient stimuli. Although epigenetic regulation and memory are inherently linked, it is currently unclear which epigenetic regulators have also a role in cellular memory. If an epigenetic mechanism has simply an instructive role, then any changes arising from its perturbation would be fully reversed once the perturbation is removed. Conversely, if a mechanism functions in cellular memory, its transient perturbation will lead to long-lasting changes. To test this idea, we subjected mouse embryonic stem cells (mESCs) to transient chromatin perturbations that disrupt the epigenome and chromosome conformation. We found that while nearly all transcriptomic changes are readily reversed, genome conformation retains a partial memory of the past perturbation even through cell division. However, when the same cells were exposed to the same perturbation during differentiation, long-lasting consequences on cell fate could be observed. In mouse gastruloids - 3D aggregates of ESCs that display key features of early postimplantation development - transient histone deacetylase inhibition leads to the expansion of the neural lineage. Thus, these results identify 3D genome folding as a mechanism of cellular memory and highlight fundamental differences in the roles that cellular memory plays at different developmental states.

Mots-Clés: Genome folding, cellular memory, chromatin states, embryonic stem cells

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