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The histone variant H3.3 and its chaperone DAXX preserve heterochromatin integrity of embryonic pluripotent cells.

Within the nucleus, heterochromatin domains segregate in particular compartments such as the chromocenters that contain pericentromeric heterochromatin (PCH) regions, or the lamina-associated domains (LADs) that localize at the periphery of the nucleus. In most cell types, DNA methylation is essential for heterochromatin formation, directly contributing to the transcriptional repression of DNA repeats and the maintenance of genome stability. Active DNA demethylation during early embryogenesis is a critical step for development but requires alternative pathways to maintain heterochromatin. Yet, the functional importance of heterochromatin and the molecular factors involved remain elusive.

Here, we address the role of DAXX, the H3.3-specific chaperone for heterochromatin deposition, in heterochromatin maintenance in Embryonic Stem Cells (ESCs). We observe that DAXX is essential for ESCs survival when grown in low DNA methylation conditions. Upon active DNA demethylation-mediated damages, DAXX relocalizes to PCH, and recruits H3.3, PML and SETDB1 to promote heterochromatin formation. In DAXX knock-out ESCs, the 3D-architecture and the physical properties of pericentric heterochromatin are impaired, resulting in overexpression of major satellite RNA. By using epigenome editing tools, we demonstrate that H3.3 and its modification on the lysine 9 directly contribute to PCH spatial conformation.

Altogether, our results demonstrate that DAXX and H3.3 are essential for the maintenance of heterochromatin in response to DNA damages in pluripotent stem cells.

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