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The histone H3.3 chaperone DAXX contributes to heterochromatin organization and protects genome integrity of 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 DNA hypomethylation, DAXX relocalizes to PCH, and recruits H3.3, PML and SETDB1 to promote heterochromatin formation. In DAXX knock-out ESCs, the formation of pericentric and peripheral heterochromatin is affected, resulting in overexpression of DNA repeats and activation of DNA damage signaling. By using epigenome CRISPR editing tools, we demonstrate that targeted upregulation of DNA repeats is sufficient to trigger DNA damage response. Additionally, our data support a role for DAXX in reforming heterochromatin after DNA damage repair.

Altogether, our results demonstrate that DAXX is essential for the maintenance of heterochromatin and protects genome integrity of pluripotent stem cells.

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