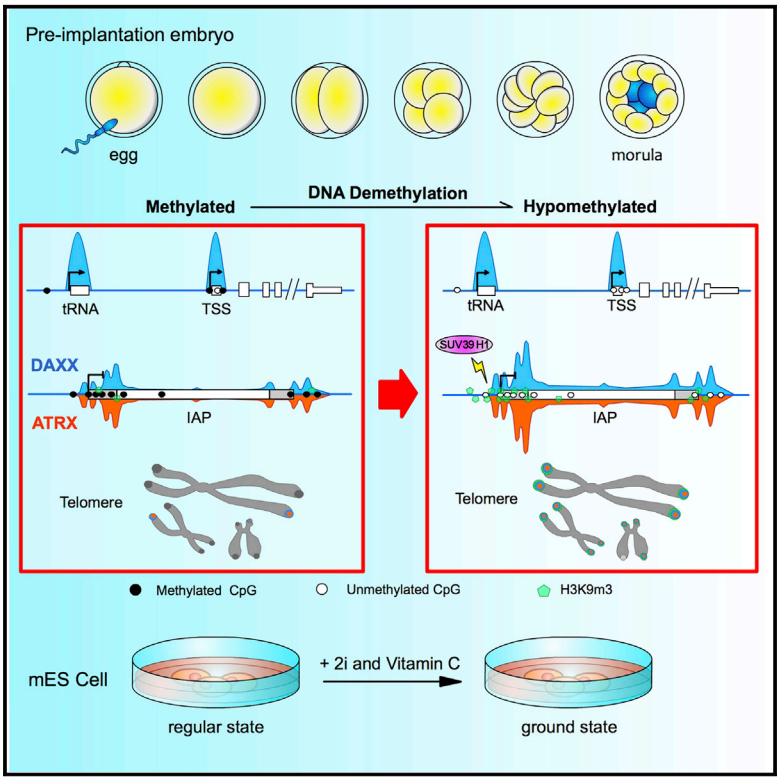
Article

Cell Stem Cell

The Daxx/Atrx Complex Protects Tandem Repetitive Elements during DNA Hypomethylation by Promoting H3K9 Trimethylation

Graphical Abstract



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In Brief

He et al. show that the chromatin factors Daxx and Atrx act as a safeguard for the genome by preventing aberrant transcription and recombination at repetitive elements and telomeres during developmental stages when global genomic DNA methylation is reduced.

Highlights

- Loss of DNA methylation increases DNA binding by Daxx and Atrx
- Knockdown of Daxx/Atrx leads to de-repression of repetitive elements
- Daxx/Atrx targeting also protects telomeres from recombination
- Daxx/Atrx recruits Suv39h to promote H3K9 trimethylation

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The Daxx/Atrx Complex Protects Tandem Repetitive Elements during DNA Hypomethylation by Promoting H3K9 Trimethylation

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SUMMARY

In mammals, DNA methylation is essential for protecting repetitive sequences from aberrant transcription and recombination. In some developmental contexts (e.g., preimplantation embryos) DNA is hypomethylated but repetitive elements are not dysregulated, suggesting that alternative protection mechanisms exist. Here we explore the processes involved by investigating the role of the chromatin factors Daxx and Atrx. Using genome-wide binding and transcriptome analysis, we found that Daxx and Atrx have distinct chromatin-binding profiles and are co-enriched at tandem repetitive elements in wild-type mouse ESCs. Global DNA hypomethylation further promoted recruitment of the Daxx/Atrx complex to tandem repeat sequences, including retrotransposons and telomeres. Knockdown of Daxx/Atrx in cells with hypomethylated genomes exacerbated aberrant transcriptional de-repression of repeat elements and telomere dysfunction. Mechanistically, Daxx/Atrx-mediated repression seems to involve Suv39h recruitment and H3K9 trimethylation. Our data therefore suggest that Daxx and Atrx safeguard the genome by silencing repetitive elements when DNA methylation levels are low.

INTRODUCTION

DNA methylation is tightly regulated by the de novo DNA methyltransferases DNMT3a/3b and the maintenance DNA methyltransferase DNMT1, and it is required for somatic cell growth and survival in mammals (Jackson-Grusby et al., 2001; Tsumura et al., 2006). DNA methylation can inhibit gene transcription and facilitate the formation of compact and inactive chromatin or heterochromatin (e.g., repetitive elements) to safeguard genome integrity and stability (Armour et al., 1996; Branzei and Foiani, 2010; Chan et al., 2006; Pathak and Ali, 2012; Jurka et al., 2007; Ross et al., 2010; Sakaue et al., 2010; Treangen and Salzberg, 2012). Repeat elements such as telomeres and centromeres are located in specific regions and are critical for maintaining the structure and integrity of chromosomes. The dysregulation of these sequences has been directly linked to genome instability and human diseases (Bzymek and Lovett, 2001; Heartlein, 1990; Mattick and Makunin, 2006). Other repeat elements such as long-terminal repeats (LTRs) containing retrotransposons (or endogenous retroviruses [ERVs]) are scattered throughout the genome. Increasing evidence indicates that these elements also possess the capacity to contribute to malignant transformation (Gao et al., 2008; Lee et al., 2012). It has been shown that ERVs are normally actively suppressed through chromatin maintenance mechanisms such as DNA methylation and histone modifications (Rebollo et al., 2012; Shalginskikh et al., 2013; Wolf et al., 2013), the disruption of which can have serious consequences and lead to diseases and cancer in humans (Bourc'his and Bestor, 2004; Dodge et al., 2005; Gaudet et al., 2003; Jackson-Grusby et al., 2001; Lewis et al., 2010; Lovejoy et al., 2012; Ross et al., 2010; Wilson et al., 2007).

Interestingly, embryonic stem cells (ESCs) can tolerate global loss of DNA methylation. Mammalian genomic DNA undergoes programmed genome-wide demethylation during specific developmental stages. For example, the vast majority of genomic DNA loses methylation due to restricted DNMT1 mobility and low DNMT3a/3b expression in preimplantation embryos (two- to eight-cell stage) and during primordial germ cell (PGC) specification (Cirio et al., 2008; Grohmann et al., 2005; Howell et al., 2001). Mouse ESCs (mESCs) deficient for Dnmts are also able to survive and maintain their self-renewal capacity (Jackson et al., 2004; Tsumura et al., 2006). Despite risks such as de-repression of repetitive elements, such genome-wide DNA demethylation does not lead to genomic instability (Baumann et al., 2010; Hutnick et al., 2010; Reik et al., 2001; Seisenberger et al., 2012), suggesting the existence of additional control mechanisms that ensure genome integrity and stability.