Novel function of HP1, a protein responsible for chromosome aggregation

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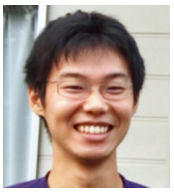

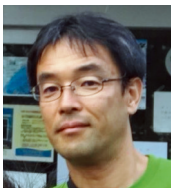

Abstract

Eukaryotic chromosomes consist of DNA and histone proteins. Chemical modifications to histones, such as methylation and acetylation, induce chromosome aggregation and relaxation, thereby altering gene expression patterns. HP1 has been identified as a binding protein for H3K9 methylation and plays a role in promoting chromosome aggregation. Because there are three paralogous of HP1 proteins in mammals, we established cells lacking all three HP1s by genome editing technology and compared them with normal cells. We found that H3K9 methyltransferases and demethylases were drastically degraded in the HP1-deficient cells, and the chromosomes could not adopt the correct structure (Fig. 1). Analysis of HP1 mutants partially lacking its function revealed that HP1 tethers H3K9 methyltransferases and demethylases to chromatin and prevents these enzymes from degradation (Fig. 2).

Background & Results

H3K9 methylation is an epigenetic mark of transcriptional silencing. HP1 was identified as an H3K9 methylation-binding protein. In mammals, HP1 is encoded by three similar genes, and previously, no significant phenotypes have been observed in cells lacking any two types of HP1. To understand the true function of HP1, we established and analyzed cells deficient in all three HP1s.

First, we focused on the fact that HP1 binds to H3K9 methyltransferase. Based on previous studies showing that H3K9 methyltransferases that cannot bind to HP1 are unstable, we hypothesized that HP1 may be involved in the protein stability of H3K9 methyltransferase. We established mouse ES cells lacking all three HP1s by a genome editing technology and found that H3K9 methyltransferase proteins was drastically reduced. We also found that HP1-depleted cells contained neither typical condensed genomic structure nor typical relaxed genomic structure (Fig. 1). These results indicate that HP1 stabilizes H3K9 methyltransferases and is essential for the maintenance of chromosome structure.

To elucidate how HP1 stabilizes H3K9 methyltransferases, we performed biochemical analyses using HP1 mutants, which can bind to H3K9 methyltransferases but not to H3K9 methylation. As a result, stabilization of these enzymes requires not only binding of HP1 to the enzyme, but also binding of HP1 to the chromosome. Moreover, we elucidated that HP1 also stabilizes H3K9 demethylase.

These results propose that HP1 serves as a hub that connects and stabilizes H3K9 methyltransferases and demethylases to chromosomes(Fig. 2).

Significance of the research and Future perspective

Our study reveals that the binding of HP1 to H3K9 methyltransferases and demetylases is essential for stabilizing these enzymes. Ectopic distribution of H3K9 methylation is observed in various diseases such as cancer. We believe that the development of drugs that inhibit or promote HP1-H3K9 methyltransferase interaction will enable us to propose treatments for diseases caused by abnormalities in H3K9 methylation.

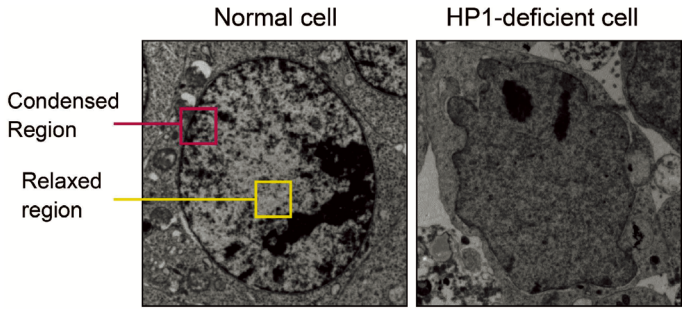

Figure 1. Comparison of nuclei of normal cells and HP1-deficient cells by electron microscopy.
Nuclei of a normal cells (left) had intensely stained condensed regions (pink area) and weakly stained relaxed regions (yellow area) that were distributed mutually exclusively. In contrast, nuclei of HP1-depleted cells (right) were uniformly stained with intermediate intensity of these regions.

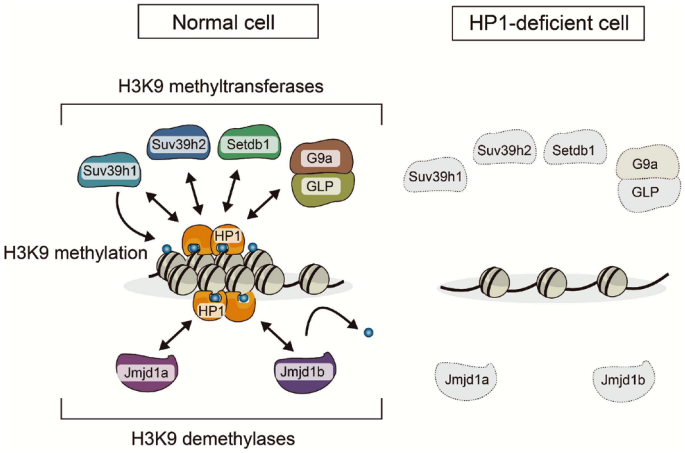

Figure 2. Functions of HP1 revealed in this study.
HP1 stabilizes H3K9 methyltransferases and demethylases by tethering them into chromatin (left); loss of HP1 leads to degradation of these enzymes and disruption of chromosome structure (right).

Patent

Treatise Maeda, Ryo; Tachibana, Makoto. HP1 maintains protein stability of H3K9 methyltransferases and demethylases. EMBO Rep. 2022, e53581. doi: 10.15252/embr.202153581

URL

Keyword chromosome, gene regulation, histone modification