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Critical determinants of mitotic bookmarking by the major notch signalling effector RBPJ

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Extended Abstract

Introduction: Cell identity maintenance requires the faithful propagation of specific transcription programs through mitosis and transcription factors selectively retained on mitotic chromatin have emerged as critical players for this process, termed mitotic bookmarking factors. We identified RBPJ, the major transcriptional effector of Notch Signaling, as one of the very few sequence-specific transcription factors retained on the mitotic chromatin of mouse embryonal carcinoma F9 cells. ChIP-seq revealed that only 60% of the chromosomal sites occupied by RBPJ in interphase cells are retained in mitotic cells. As with other bookmarking factors, how RBPJ is selectively retained at a subset of its interphase-binding sites during mitosis is entirely unknown. We hypothesized that RBPJinteracting proteins might contribute to this selective mitoticchromatin retention. RBPJ is known to interact with the histone deacetylase HDAC1 and histone demethylase KDM5A. ChIPqPCR demonstrated that HDAC1 and KDM5a associate with RBPJ binding sites in an RBPJ-dependent manner. Intriguingly, HDAC1 knockdown resulted in an increase of RBPJ occupancy in mitotic cells, indicating that HDAC1 negatively regulates RBPJ-mitotic chromatin association. Similar results were found in cells treated with the histone deacetylase inhibitor TSA.

Remarkably, we also found increased mitotic KDM5a occupancy at sites of mitotic chromatin that displayed increased RBPJ occupancy in HDAC1 KD or TSA treated cells. Knockdown of KDM5a in TSA-treated cells reversed this effect, indicating that KDM5a positively regulates increased RBPJ-mitotic chromatin association in the context of HDAC1 KD or TSA treatment. To understand further the mechanisms that retain RBPJ on mitotic chromatin, we investigated the status of histone posttranslational modifications.

Conclusion: We found that increased RBPJ occupancy is associated with decreased tri-methylation and increased mono-methylation on histone H3 lysine 4. Together, these results uncover a regulatory mechanism that can lead to the selective retention of transcription factors on mitotic chromatin.

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