Critical Determinants of Mitotic Bookmarking by the Major Notch Signaling Effector RBPJ

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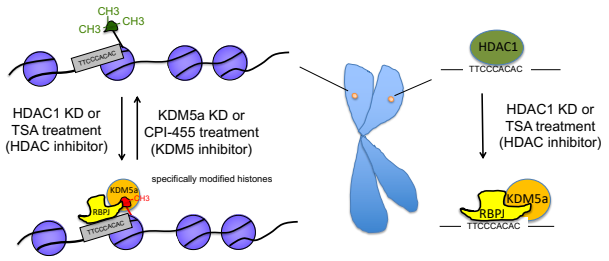
Abstract (300 word limit)

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 RBPJ-interacting proteins might contribute to this selective mitotic-chromatin retention. RBPJ is known to interact with the histone deacetylase HDAC1 and histone demethylase KDM5A. ChIP-qPCR 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. 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.

Image

Regulation of mitotic RBPJ Bookmarking by HDAC1 and KDM5a



Recent Publications (minimum 5)

1. Lake, R. J., Tsai, P.-F., Choi, I., Won, K.-J., and **Fan, H.-Y**.; RBPJ, the major transcriptional effector of Notch signaling, remains associated with chromatin throughout mitosis, suggesting a role in mitotic bookmarking; PLoS Genetics 10(3): e1004204, 2014.
2. Lee, J. Y., Lake, R. J., Kirk, J., Bohr, V. A., **Fan, H.-Y**.* and Hohng, C.*; NAP1L1 accelerates activation and decreases pausing to enhance nucleosome remodeling by CSB; Nucleic Acids Res. 45(8):4696-4707, 2017. (* Corresponding authors).
3. Lake, R.J., Boetefuer, E.L., Won, K.J. and **Fan, H.-Y**. The CSB chromatin remodeler and CTCF architectural protein cooperate in response to oxidative stress. Nucleic Acids Res. 44(5) 2125-35, 2016.
4. Lake, R.J., Boetefuer, E.L. Tsai, P.-F., Jeong, J., Choi, I., Won, K.-J., and **Fan, H.-Y.;** The sequence-specific transcription factor c-Jun targets Cockayne syndrome protein B to regulate transcription and chromatin structure; PLoS Genetics 10(4): e1004284, 2014.
5. Cho, I., Tsai, P.-F., Lake, R. J., Basheer, A., and **Fan, H.-Y**.; ATP-dependent chromatin remodeling by Cockayne Syndrome protein B and NAP1-like histone chaperones is required for efficient transcription-coupled DNA repair; PLoS Genetics 9(4): e1003407, 2013.

Biography (150 word limit)



Dr. Fan is an Associate Professor in the Program of Cancer Genetics, Epigenetics and Genomics in the University of New Mexico Comprehensive Cancer Center since 2017. Dr. Fan was an Assistant Professor in the Department of Biochemistry and Biophysics and a Core Member of the Epigenetics Program at the University of Pennsylvania Perelman School of Medicine between 2010-2017. She is interested in the field of Epigenetics and her research is currently focused in two main directions: (I) to understand how the unique and overlapping biochemical activates of different ATP-dependent chromatin remodelers are used to shape the epigenetic landscape to allow specific biological processes to ensue, and how defects in these activities can lead to disease, such as cancer, and (II) to unravel epigenetic mechanisms that maintain cell-fate commitment and lineage fidelity through mitosis via Notch signaling. She received her Ph.D from New York University, New York, USA, and did her postdoctoral training with Dr. Alan Weiner at Yale University and with Dr. Robert E. Kingston Mass General Hospital/Harvard University. She was a Howard Temin fellow between 2003-2008.

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Notes/Comments: