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Mrg15 stimulates H3K36 methyl transferase activity of Ash1 and facilitates Trithorax group protein function of Ash1 in Drosophila

Zhuqiang Zhang
Chinese Academy of Sciences, China

Ash1 is a classic Trithorax group protein that possesses H3K36-specific histone methyltransferase activity. Ash1 plays a critical role in antagonizing Polycomb silencing, and loss-of-function mutations lead to the inactivation of certain Hox genes and homeotic transformation. Here, we report the purification of the Ash1 complex and the identification of two novel subunits, Mrg15 and Nurf55. Interestingly, Mrg15 stimulates the enzymatic activity of Ash1 *in vitro*, and this stimulation is independent of the chromo domain of Mrg15. *In vivo*, Mrg15 is recruited by Ash1 to their common target genes, and Mrg15 is essential for the proper deposition of H3K36me2 at these regions. To dissect the functional role of Mrg15 in the context of the Ash1 complex and because Mrg15 is a shared partner of several chromatin-modifying enzymes, we identified an Ash1 point mutation (Ash1-R1288A) that displayed a greatly attenuated interaction with Mrg15. Knock-in flies bearing this mutation displayed multiple homeotic transformation phenotypes, and these phenotypes could be partially rescued by overexpressing the Mrg15-Nurf55 fusion protein, which stabilized the association of Mrg15 with Ash1. In summary, we identified Mrg15 as a subunit of the Ash1 complex, a stimulator of Ash1 enzymatic activity and a critical regulator of the TrxG protein function of Ash1 in Drosophila.

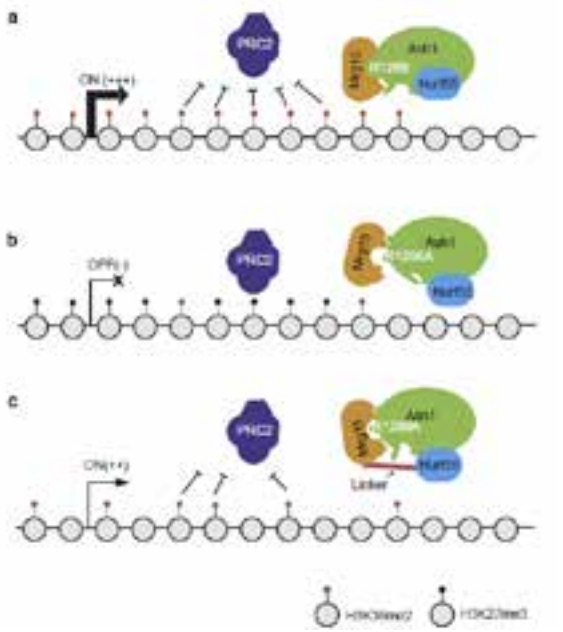

Figure 1: Model of Mrg15's role in Ash1 complex. (a) Wild-type Ash1 stably interacts with Mrg15 and becomes activated to produce adequate amounts of H3K36me2 that antagonizes Polycomb silencing at the common targets of Ash1 and Mrg15. (b) Ash1R1288A mutation greatly weakens its interaction with Mrg15 and impairs Mrg15-mediated activation, which causes the failure of anti silencing. (c) Expression of Mrg15-Nurf55 fusion protein partially restores the activation and anti silencing function of Ash1R1288A mutant.

Recent Publications

1. Xiong J, Zhang Z, Zhu B, et al. (2016) Cooperative action between SALL4A and TET proteins in stepwise oxidation of 5-methylcytosine. Molecular Cell 64(5):913-25.
2. Liu N, Zhang Z, Wu H, Zhu B, et al. (2015) Recognition of H3K9 methylation by GLP is required for efficient

establishment of H3K9 methylation, rapid target gene repression, and mouse viability. Genes & Development 29(4):379-93.

3. Mao Z, Pan L, Wang W, Zhang Z, Zhu B, Zhou Z, et al. (2014) Anp32e, a higher eukaryotic histone chaperone directs preferential recognition for H2A.Z. Cell Research 24(4):389-99.
4. Huang C, Zhang Z, Zhu B, et al. (2013) H3.3-H4 tetramer splitting events feature cell-type specific enhancers. PLoS Genetics 9(6):e1003558.

Biography

Zhuqiang Zhang completed his BS from College of Life Sciences, Beijing University, Beijing, China during 1998-2002 and his PhD in Physiology from the Institute of Zoology, CAS, China during 2002-2010. He pursued his Postdoctoral studies from National Institute of Biological Sciences (NIBS), Beijing during 2010-2014. He is currently an Associate Professor in the Institute of Biophysics, CAS, China since 2014. His research interests are focused on the understanding of establishment and inheritance of epigenetic modifications, and novel pathways in gene repression by DNA methylation, using biochemical and epigenomic techniques.

zhangzhuqiang@ibp.ac.cn

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