Molecular Cell
Article

Distinct Stimulatory Mechanisms Regulate the Catalytic Activity of Polycomb Repressive Complex 2

Chul-Hwan Lee,[1,2,5] Marlene Holder,[3,5] Daniel Grau,[3] Ricardo Saldaña-Meyer,[1,2] Jia-Ray Yu,[1,2] Rais Ahmad Ganai,[1,2] Jenny Zhang,[3] Miao Wang,[3] Gary LeRoy,[1,2] Marc-Werner Dobenecker,[4] Danny Reinberg,[1,2,*] and Karim-Jean Armache[3,6,*]

[1]Department of Biochemistry and Molecular Pharmacology, New York University School of Medicine, New York, NY 10016, USA
[2]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
[3]Skirball Institute of Biomolecular Medicine, Department of Biochemistry and Molecular Pharmacology, New York University School of Medicine, New York, NY 10016, USA
[4]Laboratory of Immune Cell Epigenetics and Signaling, The Rockefeller University, New York, NY 10065, USA
[5]These authors contributed equally
[6]Lead Contact
*Correspondence: danny.reinberg@nyumc.org (D.R.), karim-jean.armache@med.nyu.edu (K.-J.A.)
https://doi.org/10.1016/j.molcel.2018.03.019

SUMMARY

The maintenance of gene expression patterns during metazoan development is achieved, in part, by the actions of polycomb repressive complex 2 (PRC2). PRC2 catalyzes mono-, di-, and trimethylation of histone H3 at lysine 27 (H3K27), with H3K27me2/3 being strongly associated with silenced genes. We demonstrate that EZH1 and EZH2, the two mutually exclusive catalytic subunits of PRC2, are differentially activated by various mechanisms. Whereas both PRC2-EZH1 and PRC2-EZH2 are able to catalyze mono- and dimethylation, only PRC2-EZH2 is strongly activated by allosteric modulators and specific chromatin substrates to catalyze trimethylation of H3K27 in mouse embryonic stem cells (mESCs). However, we also show that a PRC2-associated protein, AEBP2, can stimulate the activity of both complexes through a mechanism independent of and additive to allosteric activation. These results have strong implications regarding the cellular requirements for and the accompanying adjustments in PRC2 activity, given the differential expression of EZH1 and EZH2 upon cellular differentiation.

INTRODUCTION

Polycomb group (PcG) proteins are key epigenetic regulators that maintain transcriptional repression of lineage-specific genes throughout metazoan development, thereby contributing to the integrity of cell identity (Liang and Zhang, 2013). In particular, PRC2 is responsible for the methylation of lysine 27 within histone H3 (H3K27me), with H3K27me3 being a hallmark of facultative heterochromatin (Margueron and Reinberg, 2011). PRC2 consists of three core subunits: one of two isoforms of Enhancer of zeste (EZH1 and -2), embryonic ectoderm development (EED), and Suppressor of zeste 12 (SUZ12). PRC2 core subunits are associated with a histone binding protein: retinoblastoma-associated proteins 46 or 48 (RBAP46/48). The EZH1/2 subunit contains a SET domain that possesses histone methyltransferase (HMT) activity. However, EZH2 in isolation exhibits an autoinhibitory conformation, which is relieved upon its interaction with EED and SUZ12 (Jiao and Liu, 2015).

The catalytic activity of PRC2 is regulated by many factors, including allosteric activators, incorporation of its different catalytic subunits (EZH1 and -2), interactions with various histone modifications or chromatin structures, and PRC2-interacting partners, including DNA and RNA (Holoch and Margueron, 2017). The mechanism conveying allosteric activation of PRC2 was revealed by the crystal structures of PRC2 (Brooun et al., 2016; Jiao and Liu, 2015; Justin et al., 2016). The final product of PRC2 catalysis, H3K27me3, is recognized by the aromatic cage of its EED subunit (Margueron et al., 2009). This interaction induces a conformational change in PRC2 that specifically activates the EZH2 enzyme. Of note, this conformational change is distinct from that involving EZH2 relief from autoinhibition through its interaction with EED and SUZ12. The hallmark of allosteric activation entails the interaction between the stimulatory responsive motif (SRM) of EZH2 and its SET-I domain (subdomain of SET), resulting in the overall stabilization of the SET domain. The proposed model of this positive feedback loop involves initial H3K27me3 deposition by PRC2; further PRC2 recruitment through binding of its EED subunit to H3K27me3, leading to allosteric activation of PRC2; and, thus, additional H3K27me3 deposition, giving rise to stable chromatin domains (Margueron et al., 2009; Oksuz et al., 2018).

EZH1 and EZH2 are the PRC2 paralogs that contain the catalytic SET domain and are mutually exclusive when forming a complex with other PRC2 core subunits (Margueron et al., 2008). The catalytic activity of PRC2 containing EZH2 (PRC2-EZH2) is greater than that of PRC2 containing EZH1 (PRC2-EZH1). By contrast, PRC2-EZH1 possesses higher affinity to nucleosomes and can generate compacted chromatin