PRC2 methylates histones and DNA

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20/07/2019
Introduction

Reactome is an open-source, open-access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 69

This document contains 1 pathway and 4 reactions (see Table of Contents)

https://www.reactome.org
PRC2 methylates histones and DNA

Stable identifier: R-HSA-212300

Compartments: nucleoplasm

Polycomb group proteins are responsible for the heritable repression of genes during development (Lee et al. 2006, Ku et al. 2008, reviewed in Simon and Kingston 2009, Margueron and Reinberg 2011, Di Croce and Helin 2013). Two major families of Polycomb complexes exist: Polycomb Repressive Complex 1 (PRC1) and Polycomb Repressive Complex 2 (PRC2). PRC1 and PRC2 each appear to comprise sets of distinct complexes that contain common core subunits and distinct accessory subunits (reviewed in Nayak et al. 2011). PRC2, through its component EZH2 or, in some complexes, EZH1 produces the initial molecular mark of repression, the trimethylation of lysine-27 of histone H3 (H3K27me3). How PRC2 is initially recruited to a locus remains unknown, however cytosine-guanine (CpG) motifs and transcripts have been suggested. Different mechanisms may be used at different loci. The trimethylated H3K27 produced by PRC2 is bound by the Polycomb subunit of PRC1. PRC1 ubiquitinates histone H2A and maintains repression.

Literature references


## Editions

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Polycomb Repressive Complex 2 (PRC2) Is recruited to chromatin

**Location:** PRC2 methylates histones and DNA

**Stable identifier:** R-HSA-212252

**Type:** omitted

**Compartments:** nucleoplasm

The core of the Polycomb Repressor Complex 2 (PRC2) contains EZH2, EED, SUV12, RpAp46, and RpAp48 (Kuzumichev et al. 2002, Cao et al. 2002). PRC2 complexes at different sites in the genome contain the core subunits plus different accessory subunits. In Drosophila PRC2 is recruited to chromatin by specific DNA sequences. In vertebrates PRC2 appears to be recruited to chromatin through several mechanisms: some (about 20%) of noncoding RNAs tethered to the locus of origin recruit PRC2 via the RNA-binding activity of EZH2 (Zhao et al. 2008, Khalil et al. 2009), GC-rich sequence elements in DNA (Mendenhall et al. 2010) and poly(ADP-ribosyl) polymerase at sites of DNA damage (Chou et al. 2010) can also recruit polycomb components. The DNA-binding proteins JARID2, AEBP2, and YY1 recruit PRC2 (Pasini et al. 2010, Li et al. 2010, reviewed in Kim and Kim 2012). The EED subunit of PRC2 can bind existing trimethylated lysine-27 on histone H3 of PRC2 which may provide a mechanism for propagation of trimethylated lysine-27 during DNA replication (Xu et al. 2010).

**Followed by:** PRC2 recruits DNA methyltransferases, PRC2 trimethylates histone H3 at lysine-27

**Literature references**


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**PRC2 trimethylates histone H3 at lysine-27**

**Location:** PRC2 methylates histones and DNA

**Stable identifier:** R-HSA-212263

**Type:** transition

**Compartments:** nucleoplasm

EZH2, a SET domain protein, trimethylates histone H3 at lysine 27 (H3K27) and lysine 9 (H3K9) (Kuzmichev et al. 2002, Cao et al. 2002, Kuzmichev et al. 2004, Martin et al. 2006, McCabe et al. 2012, Swalm et al. 2013). EZH2 has greater activity with lysine residues that have fewer methyl groups (u-demethylated:monomethylated:dimethylated=9:6:1, McCabe et al. 2012). EZH1 rather than EZH2 is present in some PRC2 complexes and can also catalyze the trimethylation of H3K27 (inferred from mouse in Shen et al. 2008), however EZH1 is also able to repress transcription without methylating histone H3 (Margueron et al. 2008).

**Preceded by:** Polycomb Repressive Complex 2 (PRC2) Is recruited to chromatin

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PRC2 recruits DNA methyltransferases

**Location:** PRC2 methylates histones and DNA

**Stable identifier:** R-HSA-212222

**Type:** binding

**Compartments:** nucleoplasm

In tumor cells the Polycomb Repressor Complex 2 associates with a DNA methyltransferase (DNMT) via the N-terminal region of EZH2 (Vire et al. 2006). DNMT1, DNMT3a, and DNMT3b can each bind EZH2 though only one is bound at any time. As inferred from mouse (Rush et al. 2009), EZH2 tethered to a locus is able to recruit Dnmt3a but additional factors may be required to trigger de novo DNA methylation. It is unknown if the DNMT is recruited only after PRC2 has been targeted to a locus.

**Preceded by:** Polycomb Repressive Complex 2 (PRC2) Is recruited to chromatin

**Followed by:** DNMT1,3A,3B:PRC2 methylates cytosine and histone H3

**Literature references**


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DNA methyltransferases (DNMTs) associate with EZH2 of the Polycomb Repressive Complex 2 (PRC2) and methylate the 5 position of the cytosine ring in DNA (Vire et al. 2006). The histone methyltransferase activity of EZH2 also trimethylates lysine-27 of histone H3 (H3K27me3). The promoters of the MYT, WNT1, KCNA1, and CNR1 genes are methylated on cytosine by the DNMT:PRC2 complex however not all loci that have H3K27me3 by PRC2 also have cytosine methylation (Vire et al. 2006, Brinkman et al. 2012). DNA methylation and H3K27me3 appear to be mutually exclusive in CpG islands but are compatible throughout most of the rest of the genome (Brinkman et al. 2012). In mouse, DNA methylation and H3K27me3 appear to be antagonistic at most loci: loss of DNA methylation causes increased H3K27me3 while loss of PRC2 has little effect on DNA methylation (Hagarman et al. 2013). By competing with DNMT3a,b for association with PRC2, DNMT3L may antagonize DNA methylation at sites bound by PRC2 (Neri et al. 2013).

**Preceded by:** PRC2 recruits DNA methyltransferases

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