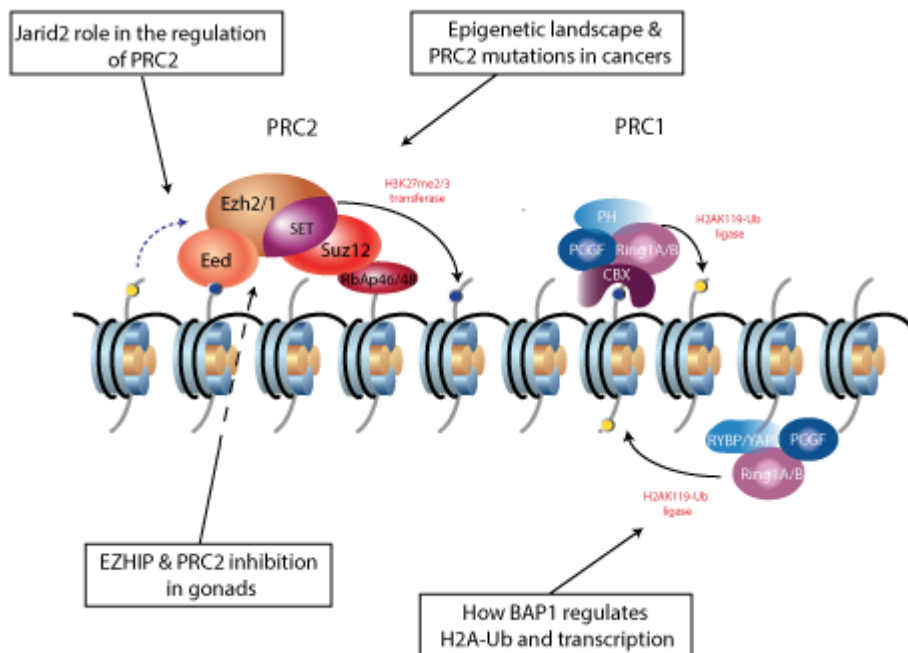




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The control of cell identity entails a precise orchestration of gene expression programs. The processes that control gene expression are responsible for generating distinct cellular identities from a single genome. Although transcription factors play a crucial role in the establishment and maintenance of transcriptional networks, their

action is modulated by chromatin. This nucleoproteic structure is regulated by the combination of histone modifications, DNA methylation, histone variant deposition and nucleosome occupancy. The precise arrangement of these chromatin modifications is governed by a battery of enzymes, whose activity must be controlled precisely and dynamically.

The Polycomb machinery plays an important role in the maintenance of cell identity by promoting a chromatin state refractory to gene expression. It is composed of several families of multiprotein complexes that are proposed to work together to maintain repression (Figure 1). The two major complexes are PRC1 and PRC2, standing for Polycomb Repressive Complex 1 and 2 respectively.

PRC2 is a four-polypeptide complex, which is responsible for the deposition of H3K27me2/3. In addition to this core complex, several facultative cofactors (AEBP2, JARID2, PCL1/2/3, EPOP, EZHIP) interact with PRC2 and modulate both its enzymatic activity and its interaction with



Maintenance of Transcriptional Repression by Polycomb Proteins

U934/UMR3215 - Genetics and Developmental Biology

chromatin. We have a strong focus on the characterization of JARID2 and EZHIP (Figure 1), which respectively stimulate and limit PRC2 activity.

PRC1 complex compacts chromatin and deposits the mono-ubiquitination of histone H2A. This activity is counteracted by the BAP1 deubiquitinase complex. We are interested in determining how BAP1 limits the activity of PRC1. We are also studying the relative contributions of PRC1 and PRC2 to transcriptional repression.

Alterations in cell identity are required for neoplastic transformation. Not surprisingly, genetic mutations that affect the Polycomb machinery either directly (e.g. mutations in PRC2 enzymatic subunit) or indirectly (e.g. mutations of BAP1 or other chromatin modifiers that antagonize or cooperate with Polycomb proteins) are recurrent in cancers. We have developed various approaches to study how these mutations affect the epigenetic landscape and to try to identify novel therapeutic strategies to specifically target these cancers.

Key publications

Year of publication 2021

Daniel Holoch, Michel Wassef, Cecilia Lövkvist, Dina Zielinski, Setareh Aflaki, Bérangère Lombard, Tiphaine Héry, Damarys Loew, Martin Howard, Raphaël Margueron (2021 Nov 16)
A cis-acting mechanism mediates transcriptional memory at Polycomb target genes in mammals.

Nature genetics : [DOI : 10.1038/s41588-021-00964-2](https://doi.org/10.1038/s41588-021-00964-2)

Year of publication 2019

Roberta Ragazzini, Raquel Pérez-Palacios, Irem H Baymaz, Seynabou Diop, Katia Ancelin, Dina Zielinski, Audrey Michaud, Maëlle Givelet, Mate Borsos, Setareh Aflaki, Patricia Legoix, Pascal W T C Jansen, Nicolas Servant, Maria-Elena Torres-Padilla, Deborah Bourc'his, Pierre Fouchet, Michiel Vermeulen, Raphaël Margueron (2019 Aug 26)
EZHIP constrains Polycomb Repressive Complex 2 activity in germ cells.

Nature communications : 10 : 1-18 : [DOI : 10.1038/s41467-019-11800-x](https://doi.org/10.1038/s41467-019-11800-x)

CAMPAGNE Antoine, LEE Ming-Kang, ZIELINSKI Dina, MICHAUD Audrey, LE CORRE Stéphanie, DINGLI Florent, CHEN Hong, SHAHIDIAN Lara Z, SERVANT Nicolas, LOEW Damarys, PASMANT Eric, PISTEL-VINAY Sophie, WASSEF Michel, MARGUERON Raphaël (2019 Jan 21)
BAP1 complex promotes transcription by opposing PRC1-mediated H2A ubiquitylation

Nature Communications : 10 : 1-15 : [DOI : 10.1038/s41467-018-08255-x](https://doi.org/10.1038/s41467-018-08255-x)



Maintenance of Transcriptional Repression by Polycomb Proteins

U934/UMR3215 - Genetics and Developmental Biology

Year of publication 2017

Manuela Portoso, Roberta Ragazzini, Živa Brenčič, Arianna Moiani, Audrey Michaud, Ivaylo Vassilev, Michel Wassef, Nicolas Servant, Bruno Sargueil, Raphaël Margueron (2017 Feb 8)

PRC2 is dispensable for HOTAIR-mediated transcriptional repression.

The EMBO journal : [DOI : e201695335](https://doi.org/10.1038/embo.2016.335)

Year of publication 2016

Marie Schoumacher, Stéphanie Le Corre, Alexandre Houy, Eskeatnaf Mulugeta, Marc-Henri Stern, Sergio Roman-Roman, Raphaël Margueron (2016 Jun 9)

Uveal melanoma cells are resistant to EZH2 inhibition regardless of BAP1 status.

Nature medicine : 577-8 : [DOI : 10.1038/nm.4098](https://doi.org/10.1038/nm.4098)

Year of publication 2015

Serena Sanulli, Neil Justin, Aurélie Teissandier, Katia Ancelin, Manuela Portoso, Matthieu Caron, Audrey Michaud, Berangère Lombard, Simao T da Rocha, John Offer, Damarys Loew, Nicolas Servant, Michel Wassef, Fabienne Burlina, Steve J Gamblin, Edith Heard, Raphaël Margueron (2015 Mar 5)

Jarid2 Methylation via the PRC2 Complex Regulates H3K27me3 Deposition during Cell Differentiation.

Molecular cell : 769-83 : [DOI : 10.1016/j.molcel.2014.12.020](https://doi.org/10.1016/j.molcel.2014.12.020)