Année de 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

Résumé

Année de publication : 2015

Michel Wassef, Veronica Rodilla, Aurélie Teissandier, Bruno Zeitouni, Nadege Gruel, Benjamin Sadacca, Marie Irondelle, Margaux Charruel, Bertrand Ducos, Audrey Michaud, Matthieu Caron, Elisabetta Marangoni, Philippe Chavrier, Christophe Le Tourneau, Maud Kamal, Eric Pasmant, Michel Vidaud, Nicolas Servant, Fabien Reyal, Dider Meseure, Anne Vincent-Salomon, Silvia Fre, Raphaël Margueron (2015 Dec 6)

Impaired PRC2 activity promotes transcriptional instability and favors breast tumorigenesis.

Genes & development : 2547-62 : DOI : 10.1101/gad.269522.115

Résumé

Alterations of chromatin modifiers are frequent in cancer, but their functional consequences often remain unclear. Focusing on the Polycomb protein EZH2 that deposits the H3K27me3 (trimethylation of Lys27 of histone H3) mark, we showed that its high expression in solid tumors is a consequence, not a cause, of tumorigenesis. In mouse and human models, EZH2 is dispensable for prostate cancer development and restrains breast tumorigenesis. High EZH2 expression in tumors results from a tight coupling to proliferation to ensure H3K27me3 homeostasis. However, this process malfunctions in breast cancer. Low EZH2 expression relative to proliferation and mutations in Polycomb genes actually indicate poor prognosis and occur in metastases. We show that while altered EZH2 activity consistently modulates a subset of its target genes, it promotes a wider transcriptional instability. Importantly, transcriptional changes that are consequences of EZH2 loss are predominantly irreversible. Our study provides an unexpected understanding of EZH2's contribution to solid tumors with important therapeutic implications.

Wassef M1, Rodilla V1, Teissandier A2, Zeitouni B2, Gruel N3, Sadacca B3, Irondelle M3, Charruel M1, Ducos B4, Michaud A1, Caron M1, Marangoni E3, Chavrier P3, Le Tourneau C5, Kamal M6, Pasmant E7, Vidaud M7, Servant N2, Reyal F3, Meseure D8, Vincent-Salomon A3, Fre S1, Margueron R1. (2015 Dec 4)

Impaired PRC2 activity promotes transcriptional instability and favors breast tumorigenesis.
Genes & DevelopmentImpaired PRC2 activity promotes transcriptional instability and favors breast tumorigenesis. : DOI : 10.1101/gad.269522.115

Résumé

Abstract

Alterations of chromatin modifiers are frequent in cancer, but their functional consequences often remain unclear. Focusing on the Polycomb protein EZH2 that deposits the H3K27me3 (trimethylation of Lys27 of histone H3) mark, we showed that its high expression in solid tumors is a consequence, not a cause, of tumorigenesis. In mouse and human models, EZH2 is dispensable for prostate cancer development and restrains breast tumorigenesis. High EZH2 expression in tumors results from a tight coupling to proliferation to ensure H3K27me3 homeostasis. However, this process malfunctions in breast cancer. Low EZH2 expression relative to proliferation and mutations in Polycomb genes actually indicate poor prognosis and occur in metastases. We show that while altered EZH2 activity consistently modulates a subset of its target genes, it promotes a wider transcriptional instability. Importantly, transcriptional changes that are consequences of EZH2 loss are predominantly irreversible. Our study provides an unexpected understanding of EZH2's contribution to solid tumors with important therapeutic implications.

Stéphanie Maupetit-Méhouas, Bertille Montibus, David Nury, Chiharu Tayama, Michel Wassef, Satya K Kota, Anne Fogli, Fabiana Cerqueira Campos, Kenichiro Hata, Robert Feil, Raphael Margueron, Kazuhiko Nakabayashi, Franck Court, Philippe Arnaud (2015 Sep 25)
Imprinting control regions (ICRs) are marked by mono-allelic bivalent chromatin when transcriptionally inactive.
Nucleic acids research : 621-35 : DOI : 10.1093/nar/gkv960

Résumé

Parental allele-specific expression of imprinted genes is mediated by imprinting control regions (ICRs) that are constitutively marked by DNA methylation imprints on the maternal or paternal allele. Mono-allelic DNA methylation is strictly required for the process of imprinting and has to be faithfully maintained during the entire life-span. While the regulation of DNA methylation itself is well understood, the mechanisms whereby the opposite allele remains unmethylated are unclear. Here, we show that in the mouse, at maternally methylated ICRs, the paternal allele, which is constitutively associated with H3K4me2/3, is marked by default by H3K27me3 when these ICRs are transcriptionally inactive, leading to the formation of a bivalent chromatin signature. Our data suggest that at ICRs, chromatin bivalency has a protective role by ensuring that DNA on the paternal allele remains unmethylated and protected against spurious and unscheduled gene expression. Moreover, they provide the proof of concept that, beside pluripotent cells, chromatin bivalency is the default state of transcriptionally inactive CpG island promoters, regardless of

the developmental stage, thereby contributing to protect cell identity.

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

Résumé

Polycomb Group (PcG) proteins maintain transcriptional repression throughout development, mostly by regulating chromatin structure. Polycomb Repressive Complex 2 (PRC2), a component of the Polycomb machinery, is responsible for the methylation of histone H3 lysine 27 (H3K27me2/3). Jarid2 was previously identified as a cofactor of PRC2, regulating PRC2 targeting to chromatin and its enzymatic activity. Deletion of Jarid2 leads to impaired orchestration of gene expression during cell lineage commitment. Here, we reveal an unexpected crosstalk between Jarid2 and PRC2, with Jarid2 being methylated by PRC2. This modification is recognized by the Eed core component of PRC2 and triggers an allosteric activation of PRC2's enzymatic activity. We show that Jarid2 methylation is important to promote PRC2 activity at a locus devoid of H3K27me3 and for the correct deposition of this mark during cell differentiation. Our results uncover a regulation loop where Jarid2 methylation fine-tunes PRC2 activity depending on the chromatin context.

Année de publication : 2014

Steven Zuryn, Arnaud Ahier, Manuela Portoso, Esther Redhouse White, Marie-Charlotte Morin, Raphaël Margueron, Sophie Jarriault (2014 Aug 16)

Transdifferentiation. Sequential histone-modifying activities determine the robustness of transdifferentiation.

Science (New York, N.Y.) : 826-9 : DOI : 10.1126/science.1255885

Résumé

Natural interconversions between distinct somatic cell types have been reported in species as diverse as jellyfish and mice. The efficiency and reproducibility of some reprogramming events represent unexploited avenues in which to probe mechanisms that ensure robust cell conversion. We report that a conserved H3K27me3/me2 demethylase, JMJD-3.1, and the H3K4 methyltransferase Set1 complex cooperate to ensure invariant transdifferentiation (Td) of postmitotic Caenorhabditis elegans hindgut cells into motor neurons. At single-cell resolution, robust conversion requires stepwise histone-modifying activities, functionally partitioned into discrete phases of Td through nuclear degradation of JMJD-3.1 and phase-

specific interactions with transcription factors that have conserved roles in cell plasticity and terminal fate selection. Our results draw parallels between epigenetic mechanisms underlying robust Td in nature and efficient cell reprogramming in vitro.

Simão Teixeira da Rocha, Valentina Boeva, Martin Escamilla-Del-Arenal, Katia Ancelin, Camille Granier, Neuza Reis Matias, Serena Sanulli, Jen Chow, Edda Schulz, Christel Picard, Syuzo Kaneko, Kristian Helin, Danny Reinberg, A Francis Stewart, Anton Wutz, Raphaël Margueron, Edith Heard (2014 Jan 23)

Jarid2 Is Implicated in the Initial Xist-Induced Targeting of PRC2 to the Inactive X Chromosome.

Molecular cell : 301-16 : DOI : 10.1016/j.molcel.2014.01.002

Résumé

During X chromosome inactivation (XCI), the Polycomb Repressive Complex 2 (PRC2) is thought to participate in the early maintenance of the inactive state. Although Xist RNA is essential for the recruitment of PRC2 to the X chromosome, the precise mechanism remains unclear. Here, we demonstrate that the PRC2 cofactor Jarid2 is an important mediator of Xist-induced PRC2 targeting. The region containing the conserved B and F repeats of Xist is critical for Jarid2 recruitment via its unique N-terminal domain. Xist-induced Jarid2 recruitment occurs chromosome-wide independently of a functional PRC2 complex, unlike at other parts of the genome, such as CG-rich regions, where Jarid2 and PRC2 binding are interdependent. Conversely, we show that Jarid2 loss prevents efficient PRC2 and H3K27me3 enrichment to Xist-coated chromatin. Jarid2 thus represents an important intermediate between PRC2 and Xist RNA for the initial targeting of the PRC2 complex to the X chromosome during onset of XCI.

Chiara Mozzetta, Julien Pontis, Lauriane Fritsch, Philippe Robin, Manuela Portoso, Caroline Proux, Raphaël Margueron, Slimane Ait-Si-Ali (2014 Jan 7)

The histone H3 lysine 9 methyltransferases G9a and GLP regulate polycomb repressive complex 2-mediated gene silencing.

Molecular cell : 277-89 : DOI : 10.1016/j.molcel.2013.12.005

Résumé

G9a/GLP and Polycomb Repressive Complex 2 (PRC2) are two major epigenetic silencing machineries, which in particular methylate histone H3 on lysines 9 and 27 (H3K9 and H3K27), respectively. Although evidence of a crosstalk between H3K9 and H3K27 methylations has started to emerge, their actual interplay remains elusive. Here, we show that PRC2 and G9a/GLP interact physically and functionally. Moreover, combining different genome-wide approaches, we demonstrate that Ezh2 and G9a/GLP share an important number of common genomic targets, encoding developmental and neuronal regulators. Furthermore, we show that G9a enzymatic activity modulates PRC2 genomic recruitment to

a subset of its target genes. Taken together, our findings demonstrate an unanticipated interplay between two main histone lysine methylation mechanisms, which cooperate to maintain silencing of a subset of developmental genes.

Année de publication : 2013

Jinsook Son, Steven S Shen, Raphael Margueron, Danny Reinberg (2013 Dec 20)
Nucleosome-binding activities within JARID2 and EZH1 regulate the function of PRC2 on chromatin.
Genes & development : 2663-77 : DOI : 10.1101/gad.225888.113

Résumé

Polycomb-repressive complex 2 (PRC2) comprises specific members of the Polycomb group of epigenetic modulators. PRC2 catalyzes methylation of histone H3 at Lys 27 (H3K27me3) through its Enhancer of zeste (Ezh) constituent, of which there are two mammalian homologs: Ezh1 and Ezh2. Several ancillary factors, including Jarid2, modulate PRC2 function, with Jarid2 facilitating its recruitment to target genes. Jarid2, like Ezh2, is present in poorly differentiated and actively dividing cells, while Ezh1 associates with PRC2 in all cells, including resting cells. We found that Jarid2 exhibits nucleosome-binding activity that contributes to PRC2 stimulation. Moreover, such nucleosome-binding activity is exhibited by PRC2 comprising Ezh1 (PRC2-Ezh1), in contrast to PRC2-Ezh2. The presence of Ezh1 helps to maintain PRC2 occupancy on its target genes in myoblasts where Jarid2 is not expressed. Our findings allow us to propose a model in which PRC2-Ezh2 is important for the de novo establishment of H3K27me3 in dividing cells, whereas PRC2-Ezh1 is required for its maintenance in resting cells.

Monica Rolando, Christophe Rusniok, Raphael Margueron, Carmen Buchrieser (2013 Oct 24)
[Host epigenetic targeting by Legionella pneumophila].
Médecine sciences : M/S : 843-5 : DOI : 10.1051/medsci/20132910010

Résumé

M Escamilla-Del-Arenal, S T da Rocha, C G Spruijt, O Masui, O Renaud, Arne H Smits, R Margueron, M Vermeulen, E Heard (2013 Oct 23)
Cdyl, a new partner of the inactive X chromosome and potential reader of H3K27me3 and H3K9me2.
Molecular and cellular biology : 5005-20 : DOI : 10.1128/MCB.00866-13

Résumé

X chromosome inactivation is a remarkable example of chromosome-wide gene silencing and

facultative heterochromatin formation. Numerous histone posttranslational modifications, including H3K9me2 and H3K27me3, accompany this process, although our understanding of the enzymes that lay down these marks and the factors that bind to them is still incomplete. Here we identify Cdyl, a chromodomain-containing transcriptional corepressor, as a new chromatin-associated protein partner of the inactive X chromosome (Xi). Using mouse embryonic stem cell lines with mutated histone methyltransferase activities, we show that Cdyl relies on H3K9me2 for its general association with chromatin in vivo. For its association with Xi, Cdyl requires the process of differentiation and the presence of H3K9me2 and H3K27me3, which both become chromosomally enriched following Xist RNA coating. We further show that the removal of the PRC2 component Eed and subsequent loss of H3K27me3 lead to a reduction of both Cdyl and H3K9me2 enrichment on inactive Xi. Finally, we show that Cdyl associates with the H3K9 histone methyltransferase G9a and the MGA protein, both of which are also found on Xi. We propose that the combination of H3K9me2 and H3K27me3 recruits Cdyl to Xi, and this, in turn, may facilitate propagation of the H3K9me2 mark by anchoring G9a.

Année de publication : 2012

Monica Rolando, Serena Sanulli, Christophe Rusniok, Laura Gomez-Valero, Clement Bertholet, Tobias Sahr, Raphael Margueron, Carmen Buchrieser (2012 Dec 10)

Legionella pneumophila effector RomA uniquely modifies host chromatin to repress gene expression and promote intracellular bacterial replication.

Cell host & microbe : 395-405 : DOI : 10.1016/j.chom.2013.03.004

Résumé

Histone posttranslational modifications control eukaryotic gene expression and regulate many biological processes including immunity. Pathogens alter host epigenetic control to aid pathogenesis. We find that the intracellular bacterial pathogen Legionella pneumophila uses a Dot/Icm type IV secreted effector, RomA, to uniquely modify the host chromatin landscape. RomA, a SET domain-containing methyltransferase, trimethylates K14 of histone H3, a histone mark not previously described in mammals. RomA localizes to the infected cell nucleus where it promotes a burst of H3K14 methylation and consequently decreases H3K14 acetylation, an activating histone mark, to repress host gene expression. ChIP-seq analysis identified 4,870 H3K14 methylated promoter regions, including innate immune genes. Significantly reduced replication of a RomA-deleted strain in host cells was trans-complemented by wild-type, but not by catalytically inactive, RomA. Thus, a secreted L. pneumophila effector targets the host cell nucleus and modifies histones to repress gene expression and promote efficient intracellular replication.

Inês Pinheiro, Raphaël Margueron, Nicholas Shukeir, Michael Eisold, Christoph Fritzsch, Florian M Richter, Gerhard Mittler, Christel Genoud, Susumu Goyama, Mineo Kurokawa, Jinsook Son, Danny Reinberg, Monika Lachner, Thomas Jenuwein (2012 Sep 4)

Prdm3 and Prdm16 are H3K9me1 methyltransferases required for mammalian heterochromatin integrity.
Cell : 948-60 : DOI : 10.1016/j.cell.2012.06.048

Résumé

Heterochromatin serves important functions, protecting genome integrity and stabilizing gene expression programs. Although the Suv39h methyltransferases (KMTs) are known to ensure pericentric H3K9me3 methylation, the mechanisms that initiate and maintain mammalian heterochromatin organization remain elusive. We developed a biochemical assay and used in vivo analyses in mouse embryonic fibroblasts to identify Prdm3 and Prdm16 as redundant H3K9me1-specific KMTs that direct cytoplasmic H3K9me1 methylation. The H3K9me1 is converted in the nucleus to H3K9me3 by the Suv39h enzymes to reinforce heterochromatin. Simultaneous depletion of Prdm3 and Prdm16 abrogates H3K9me1 methylation, prevents Suv39h-dependent H3K9me3 trimethylation, and derepresses major satellite transcription. Most strikingly, DNA-FISH and electron microscopy reveal that combined impairment of Prdm3 and Prdm16 results in disintegration of heterochromatic foci and disruption of the nuclear lamina. Our data identify Prdm3 and Prdm16 as H3K9me1 methyltransferases and expose a functional framework in which anchoring to the nuclear periphery helps maintain the integrity of mammalian heterochromatin.

Philipp Tropberger, Sebastian Pott, Claudia Keller, Kinga Kamieniarz-Gdula, Matthieu Caron, Florian Richter, Guohong Li, Gerhard Mittler, Edison T Liu, Marc Bühler, Raphael Margueron, Robert Schneider (2012 Apr 4)

Regulation of transcription through acetylation of H3K122 on the lateral surface of the histone octamer.
Cell : 859-72 : DOI : 10.1016/j.cell.2013.01.032

Résumé

Histone modifications are key regulators of chromatin function. However, little is known to what extent histone modifications can directly impact on chromatin. Here, we address how a modification within the globular domain of histones regulates chromatin function. We demonstrate that H3K122ac can be sufficient to stimulate transcription and that mutation of H3K122 impairs transcriptional activation, which we attribute to a direct effect of H3K122ac on histone-DNA binding. In line with this, we find that H3K122ac defines genome-wide genetic elements and chromatin features associated with active transcription. Furthermore, H3K122ac is catalyzed by the coactivators p300/CBP and can be induced by nuclear hormone receptor signaling. Collectively, this suggests that transcriptional regulators elicit their effects not only via signaling to histone tails but also via direct structural perturbation of nucleosomes by directing acetylation to their lateral surface.

Jon Mallen-St Clair, Rengin Soydaner-Azeloglu, Kyoung Eun Lee, Laura Taylor, Alexandra Livanos, Yuliya Pylayeva-Gupta, George Miller, Raphaël Margueron, Danny Reinberg, Dafna Bar-Sagi

(2012 Mar 7)

EZH2 couples pancreatic regeneration to neoplastic progression.

Genes & development : 439-44 : DOI : 10.1101/gad.181800.111

Résumé

Although the polycomb group protein Enhancer of Zeste Homolog 2 (EZH2) is well recognized for its role as a key regulator of cell differentiation, its involvement in tissue regeneration is largely unknown. Here we show that EZH2 is up-regulated following cerulein-induced pancreatic injury and is required for tissue repair by promoting the regenerative proliferation of progenitor cells. Loss of EZH2 results in impaired pancreatic regeneration and accelerates KRas(G12D)-driven neoplasia. Our findings implicate EZH2 in constraining neoplastic progression through homeostatic mechanisms that control pancreatic regeneration and provide insights into the documented link between chronic pancreatic injury and an increased risk for pancreatic cancer.