

Année de publication : 2019

Geneviève Almouzni (2019 Apr 11)

Deciphering the mechanisms of chromatin states**Résumé**

For the EU researcher magazine, Genevieve Almouzni talks about the work of the ChromADICT project in investigating the general principles that control chromatin states, work which could lead to a deeper understanding of many pathological cases

: https://issuu.com/eu_research/docs/chromadict_eur19_h_res

Année de publication : 2018

Tejas Yadav, Jean-Pierre Quivy, Geneviève Almouzni. (2018 Sep 26)

Chromatin plasticity: A versatile landscape that underlies cell fate and identity.

Science : Vol. 361, Issue 6409:1332-1336 : [DOI : DOI: 10.1126/science.aat8950](https://doi.org/10.1126/science.aat8950)

Résumé

Chromatin plasticity: A versatile landscape that underlies cell fate and identity.

Roberto Bellelli, Ondrej Belan, Valerie E. Pye, Camille Clement, Sarah L. Maslen, J. Mark Skehel, Peter Cherepanov, Genevieve Almouzni, and Simon J. Boulton. (2018 Sep 11)

POLE3-POLE4 Is a Histone H3-H4 Chaperone that Maintains Chromatin Integrity during DNA Replication

Molecular Cell : 72, 112-126 : [DOI : DOI: https://doi.org/10.1016/j.molcel.2018.08.043](https://doi.org/10.1016/j.molcel.2018.08.043)

Résumé

POLE3-POLE4 Is a Histone H3-H4 Chaperone that Maintains Chromatin Integrity during DNA Replication

Shweta Mendiratta, Alberto Gatto, Genevieve Almouzni. (2018 Aug 28)

Histone supply: Multitiered regulation ensures chromatin dynamics throughout the cell cycle.

Journal of Cell Biology : [DOI : DOI: 10.1083/jcb.201807179](https://doi.org/10.1083/jcb.201807179)

Résumé

Histone supply: Multitiered regulation ensures chromatin dynamics throughout the cell cycle.

Camille Clément, Guillermo A. Orsi, Alberto Gatto, Ekaterina Boyarchuk, Audrey Forest, Bassam Hajj, Judith Miné-Hattab, Mickaël Garnier, Zachary A. Gurard-Levin, Jean-Pierre Quivy & Geneviève Almouzni. (2018 Aug 9)

High-resolution visualization of H3 variants during replication reveals their controlled recycling

Nature Communications : 9:31-81.

Résumé

High-resolution visualization of H3 variants during replication reveals their controlled recycling

Dominique Ray-Gallet, M. Daniel Rickett, Yukari Sato, Kushol Gupta, Ekaterina Boyarchuk, Toshiya Senda, Ronen Marmorstein & Geneviève Almouzni. (2018 Aug 6)

Functional activity of the H3.3 histone chaperone complex HIRA requires trimerization of the HIRA

Nature Communications : 9: 3103 : [DOI : DOI: 10.1038/s41467-018-05581-y](https://doi.org/10.1038/s41467-018-05581-y)

Résumé

Functional activity of the H3.3 histone chaperone complex HIRA requires trimerization of the HIRA subunit

Aaron Mendez-Bermudez, Liudmyla Lototska, Serge Bauwens, Marie-Josèphe Giraud-Panis, Olivier Croce, Karine Jamet, Agurtzane Irizar, Macarena Mowinckel, Stephane Koundrioukoff, Nicolas Nottet, Genevieve Almouzni, Mare-Paule Teulade-Fichou, Michael Schertzer, Mylène Perderiset, Arturo Londoño-Vallejo, Michelle Debatisse, Eric Gilson, Jing Ye (2018 May 3)

Genome-wide Control of Heterochromatin Replication by the Telomere Capping Protein TRF2

Molecular cell : 70 : 449-461.e5 : [DOI : 10.1016/j.molcel.2018.03.036](https://doi.org/10.1016/j.molcel.2018.03.036)

Résumé

Hard-to-replicate regions of chromosomes (e.g., pericentromeres, centromeres, and telomeres) impede replication fork progression, eventually leading, in the event of replication stress, to chromosome fragility, aging, and cancer. Our knowledge of the mechanisms controlling the stability of these regions is essentially limited to telomeres, where fragility is counteracted by the shelterin proteins. Here we show that the shelterin subunit TRF2 ensures progression of the replication fork through pericentromeric

heterochromatin, but not centromeric chromatin. In a process involving its N-terminal basic domain, TRF2 binds to pericentromeric Satellite III sequences during S phase, allowing the recruitment of the G-quadruplex-resolving helicase RTEL1 to facilitate fork progression. We also show that TRF2 is required for the stability of other heterochromatic regions localized throughout the genome, paving the way for future research on heterochromatic replication and its relationship with aging and cancer.

Année de publication : 2017

D Morel, G Almouzni, J-C Soria, S Postel-Vinay (2017 Apr 21)

Targeting chromatin defects in selected solid tumors based on oncogene addiction, synthetic lethality and epigenetic antagonism.

Annals of oncology : official journal of the European Society for Medical Oncology : 254-269 : [DOI : 10.1093/annonc/mdw552](https://doi.org/10.1093/annonc/mdw552)

Résumé

Although the role of epigenetic abnormalities has been studied for several years in cancer genesis and development, epigenetic-targeting drugs have historically failed to demonstrate efficacy in solid malignancies. However, successful targeting of chromatin remodeling deficiencies, histone writers and histone reader alterations has been achieved very recently using biomarker-driven and mechanism-based approaches. Epigenetic targeting is now one of the most active areas in drug development and could represent novel therapeutic opportunity for up to 25% of all solid tumors.

Dan Filipescu, Monica Naughtin, Katrina Podsypanina, Vincent Lejour, Laurence Wilson, Zachary A Gurard-Levin, Guillermo A Orsi, Iva Simeonova, Eleonore Toufektchan, Laura D Attardi, Franck Toledo, Geneviève Almouzni (2017 Mar 31)

Essential role for centromeric factors following p53 loss and oncogenic transformation.

Genes & development : 463-480 : [DOI : 10.1101/gad.290924.116](https://doi.org/10.1101/gad.290924.116)

Résumé

In mammals, centromere definition involves the histone variant CENP-A (centromere protein A), deposited by its chaperone, HJURP (Holliday junction recognition protein). Alterations in this process impair chromosome segregation and genome stability, which are also compromised by p53 inactivation in cancer. Here we found that CENP-A and HJURP are transcriptionally up-regulated in p53-null human tumors. Using an established mouse embryonic fibroblast (MEF) model combining p53 inactivation with E1A or HRas-V12 oncogene expression, we reproduced a similar up-regulation of HJURP and CENP-A. We delineate functional CDE/CHR motifs within the Hjurp and Cenpa promoters and demonstrate their roles in p53-mediated repression. To assess the importance of HJURP up-regulation in transformed murine and human cells, we used a CRISPR/Cas9 approach. Remarkably,

depletion of HJURP leads to distinct outcomes depending on their p53 status. Functional p53 elicits a cell cycle arrest response, whereas, in p53-null transformed cells, the absence of arrest enables the loss of HJURP to induce severe aneuploidy and, ultimately, apoptotic cell death. We thus tested the impact of HJURP depletion in pre-established allograft tumors in mice and revealed a major block of tumor progression *in vivo*. We discuss a model in which an « epigenetic addiction » to the HJURP chaperone represents an Achilles' heel in p53-deficient transformed cells.

Paul Victor Sauer, Jennifer Timm, Danni Liu, David Sitbon, Elisabetta Boeri-Erba, Christophe Velours, Norbert Mücke, Jörg Langowski, Françoise Ochsenbein, Geneviève Almouzni, Daniel Panne (2017 Mar 19)

Insights into the molecular architecture and histone H3-H4 deposition mechanism of yeast Chromatin assembly factor 1.

eLife : [DOI : 10.7554/eLife.23474](https://doi.org/10.7554/eLife.23474)

Résumé

How the very first step in nucleosome assembly, deposition of histone H3-H4 as tetramers or dimers on DNA, is accomplished remains largely unclear. Here, we report that yeast chromatin assembly factor 1 (CAF1), a conserved histone chaperone complex that deposits H3-H4 during DNA replication, binds a single H3-H4 heterodimer in solution. We identify a new DNA-binding domain in the large Cac1 subunit of CAF1, which is required for high-affinity DNA binding by the CAF1 three-subunit complex, and which is distinct from the previously described C-terminal winged-helix domain. CAF1 binds preferentially to DNA molecules longer than 40 bp, and two CAF1-H3-H4 complexes concertedly associate with DNA molecules of this size, resulting in deposition of H3-H4 tetramers. While DNA binding is not essential for H3-H4 tetrasome deposition *in vitro*, it is required for efficient DNA synthesis-coupled nucleosome assembly. Mutant histones with impaired H3-H4 tetramerization interactions fail to release from CAF1, indicating that DNA deposition of H3-H4 tetramers by CAF1 requires a hierarchical cooperation between DNA binding, H3-H4 deposition and histone tetramerization.

Christèle Maison, Jean-Pierre Quivy, Geneviève Almouzni (2017 Jan 17)

Suv39h1 links the SUMO pathway to constitutive heterochromatin.

Molecular & cellular oncology : e1225546 : [DOI : 10.1080/23723556.2016.1225546](https://doi.org/10.1080/23723556.2016.1225546)

Résumé

The Suv39h lysine methyltransferases, known as key enzymes responsible for histone H3 lysine 9 methylation, are critical for heterochromatin protein 1 enrichment at constitutive heterochromatin. Our recent findings reveal a new role for the Suv39h1 paralog that links it to SUMO pathway function at constitutive heterochromatin.

Année de publication : 2016

Sebastian Müller, Geneviève Almouzni (2016 Dec 1)

Chromatin dynamics during the cell cycle at centromeres.

Nature Reviews Genetics : 192-208 : [DOI : 10.1038/nrg.2016.157](https://doi.org/10.1038/nrg.2016.157)

Résumé

Centromeric chromatin undergoes major changes in composition and architecture during each cell cycle. These changes in specialized chromatin facilitate kinetochore formation in mitosis to ensure proper chromosome segregation. Thus, proper orchestration of centromeric chromatin dynamics during interphase, including replication in S phase, is crucial. We provide the current view concerning the centromeric architecture associated with satellite repeat sequences in mammals and its dynamics during the cell cycle. We summarize the contributions of deposited histone variants and their chaperones, other centromeric components – including proteins and their post-translational modifications, and RNAs – and we link the expression and deposition timing of each component during the cell cycle. Because neocentromeres occur at ectopic sites, we highlight how cell cycle processes can go wrong, leading to neocentromere formation and potentially disease.

Nicolas Lacoste, Wajid Bhat, Jacques Côté (2016 Nov 18)

Purification of Yeast Native Reagents for the Analysis of Chromatin Function-II: Multiprotein Complexes and Biochemical Assays.

Methods in molecular biology (Clifton, N.J.) : 53-67

Résumé

Post-translational modifications of histones play essential roles in regulating chromatin structure and function. These are tightly regulated in vivo and there is an intricate cross-talk between different marks as they are recognized by specific reader modules present in a large number of nuclear factors. In order to precisely dissect these processes in vitro native reagents like purified chromatin and histone modifying/remodeling enzymes are required to more accurately reproduce physiological conditions. The vast majority of these enzymes need to be part of stable multiprotein complexes with cofactors enabling them to act on chromatin substrates and/or read specific histone marks. In the accompanying chapter, we have described the protocol for purification of native chromatin from yeast cells (Chapter 3). Here, we present the methods to obtain highly purified native chromatin modifying complexes from *Saccharomyces cerevisiae*, based on Tandem Affinity Purification (TAP). We also present possible applications and useful functional assays that can be performed using these yeast native reagents.

Nicolas Lacoste, Wajid Bhat, Jacques Côté (2016 Nov 18)

Purification of Yeast Native Reagents for the Analysis of Chromatin Function-I:

Nucleosomes for Reconstitution and Manipulation of Histone Marks.

Methods in molecular biology (Clifton, N.J.) : 39-51

Résumé

Purification of native biological material provides powerful tools for the functional analysis of enzymes and proteins in chromatin. In particular, histone proteins harbor numerous post-translational modifications, which may differ between species, tissues, and growth conditions and are lacking on recombinant histones. Moreover, the physiological substrate of most enzymes that modify histones is chromatin and the majority of these enzymes need to be part of a multiprotein assembly to be able to act on chromatin. For the yeast *Saccharomyces cerevisiae* different chromatin purification protocols are available but often result in poor yields or rely on genetic manipulation. We present a simple purification protocol that can yield up to 150 µg of pure native chromatin per liter of yeast culture. The purified material can be obtained from mutant cells lacking specific histone modifications and can be used in *in vitro* chromatin assembly for biochemical studies. Based on the extremely high degree of conservation throughout eukaryotes, this modifiable native chromatin can be used in studies with factors from other organisms including humans.

Guillermo A Orsi, Monica Naughtin, Geneviève Almouzni (2016 Nov 5)

The Epigenome and Cancer Stem Cell Fate: Connected by a Linker Histone Variant.

Cell stem cell : 567-568 : [DOI : S1934-5909\(16\)30350-2](https://doi.org/10.1016/j.stem.2016.11.005)

Résumé

The molecular features underlying tumor heterogeneity and the role of chromatin components in regulating cell fate within tumors are not well understood. Recently in *Science*, Torres et al. (2016) showed that the linker histone variant H1.0 functions as a chromatin switch that determines self-renewal versus differentiation decisions in cancer stem cells.