Two distinct HIRA-dependent pathways handle H3.3 de novo deposition and recycling during transcription

Summary

Design on a Rational Basis of High-Affinity Peptides Inhibiting the Histone Chaperone ASF1

Summary

Combining epigenetic drugs with other therapies for solid tumours — past lessons and future promise

Summary

Dynamic Histone H3 Incorporation Fuels Metastatic Progression

Summary

Regardless of the deposition pathway, aminoacid 31 in histone variant H3 is
essential at gastrulation in Xenopus

DOI: 10.1101/612515

Summary

Geneviève Almouzni (2019 Apr 11)

Deciphering the mechanisms of chromatin states

Summary

For the EU researcher magazine, Genevieve Almouzni talks about the work of the Chro3ADICT 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

Year of publication 2018

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

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


Summary

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

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

Summary

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


Histone supply: Multitiered regulation ensures chromatin dynamics throughout
the cell cycle.
*Journal of Cell Biology*: DOI: DOI: 10.1083/jcb.201807179

**Summary**

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


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

**Summary**

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


**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

**Summary**

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

**Summary**

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.

Summary

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.


Essential role for centromeric factors following p53 loss and oncogenic transformation.
Genes & development : 463-480 : DOI : 10.1101/gad.290924.116

Summary

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.


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

eLife: DOI: 10.7554/eLife.23474

**Summary**

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.