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ITMO Cancer

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Chromatin Dynamics

/ / Almouzni Geneviève CNRS / Insitut Curie

Our team has over 20 years of expertise in chromatin and nuclear organization, replication, repair and development. We provided key contributions to understand the mechanism of chromatin assembly from its basic unit to high order structure.

Key Facts

- ***Team :***

  Researchers : 5
  Technicians : 6
  PhD students : 5
  Postdoc fellows : 9

- ***Translational approaches :***

  Patents : 4
  Clinical research grants : 14
  Industry partners : 3

- ***International research links :***

Keywords

- Chromatin dynamics
- Chaperones, Genome stability
- Centromere
- Epigenetics
- Cancer
- Imaging
- Developmental technics & cell culture
- Recombinant protein technology
- Biochemistry techniques
- Molecular biology

Biological resources

- Links with Institut Curie hospital groups :
- annotated samples, tumor library
- cohort of patients with their follow-up
- Access to Institut Curie platforms :
- high-throughput expression and sequencing
- microscopy, proteomic
- tissue array
- chemical compound array

Research brief

Chromatin organization, from its very basic unit, the nucleosome, up to higher order structures and nuclear domains, is critical for genome function (Fig. 1). The importance of this organization and its dynamics in the propagation of a cellular identity in a given cell lineage is an active area of research in the field of epigenetics. Beyond mechanisms ensuring the maintenance of the DNA sequence itself, other mechanisms of information inheritance operating at the chromatin level could be key for the development and life of an organism. Our general objectives are to establish how histone chaperones and chromatin interacting factors work together within an interactive network of assembly/disassembly lines and in coordination with an ever-changing cell metabolism (Fig. 2 & 3). We aim to determine (i) the behavior of these factors as components of dynamic complexes and (ii) how this behavior impacts on genome organization, function and stability during the cell cycle, development, in response to genotoxic stress and under both normal and pathological conditions (such as cancer)

Our research strategy comprises :

1. Elucidating the network of a histone flow during chromatin assembly
2. Exploring specific regions of the nucleus (e.g., centromeric domains)
3. Assessing chromatin integrity in the context of DNA repair
4. Determining the physiological relevance of critical factors in development and in the context of cancer

Methodologies used

- ? SNAP-tagging and imaging
- ? ChIP and ChIP-Seq
- ? RNA interference in cultured cells
- ? Protein complexes purification from cells stably expressing tagged-factors
- ? Micro-injection/manipulation of Xenopus and mouse early embryos (2 cell stage) and follow-up of development
- ? Advanced 3D and time-lapse fluorescence microscopy
- ? Transgenic/KO mouse models
- ? Bio-computing analysis of high-throuput sequencing/expression data
- ? Analysis of the dynamics of factors in vivo by SNAP-Tag and imaging including FRAP, local damage
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Publications

- Polo S., Roche D. & Almouzni G. (2006) Evidence for new histone incorporation marking sites of UV-repair in human cells. Cell, 127, 481-493.
- Groth A., Corpet A., Cook A., Roche D., Bartek J., Lukas J. & Almouzni G. (2007) Regulation of replication fork progression through histone supply/demand. Science, 318, 1928-1931.
- Dunleavy E.M., Roche D., Tagami H., Lacoste N., Ray-Gallet D., Nakamura Y., Daigo Y., Nakatani Y. & Almouzni G. (2009) HJURP, a key CENP-A-partner for maintenance and deposition of CENP-A at centromeres at late telophase/G1. Cell, 137, 485-497.
- Probst A.V., Okamoto I., Casanova M., ElMarjou F., Le Baccon P. & Almouzni G. (2010) A strand-specific burst in transcription of pericentric satellites is required for chromocenter formation and early mouse development. Dev. Cell, 19, 625-638
- Maison C., Bailly D., Roche D., Montes de Oca R., Probst A.V., Vassias I., Dingli F., Lombard B., Loew D., Quivy J.P. & Almouzni G. (2011) SUMOylation promotes de novo targeting of HP1? to pericentric heterochromatin. Nature Genet., 43, 220-227.
- Ray-Gallet D., Woolfe A., Vassias I., Pellentz C., Lacoste N., Puri A., Schultz D.C., Pchelintsev N.A., Adams P.D., Jansen L.E. & Almouzni G. (2011) Dynamics of histone H3 deposition in vivo reveal a nucleosome gap-filling mechanism for H3.3 to maintain chromatin integrity. Mol. Cell, 44, 928-941.

Patents, pending/registered

Left; water color of Nicolas Bouvier to G. Almouzni depicting the various levels of chromatin organization from a single

nucleosomes to higher order order structures in the nucleus. Right; From chromatin assembly and integrity up to nuclear organization and function, a connection that impacts genome function during normal development and in pathologies: the issue of establishment and maintenance.

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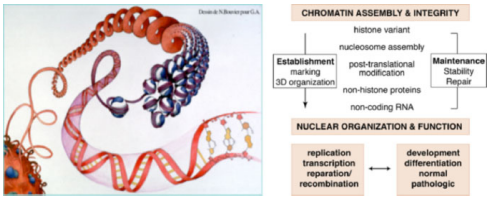
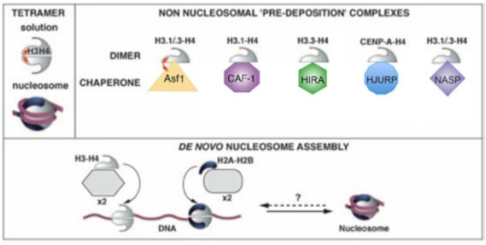
Artistic representation of chromatin organization and its impacts on nuclear function

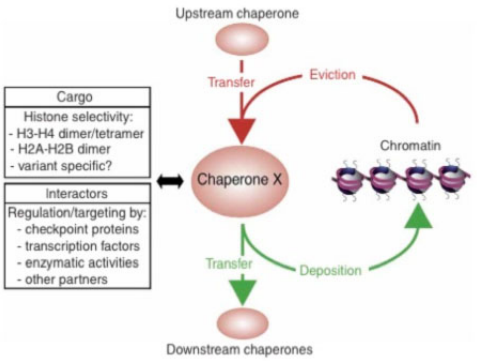


Histone chaperones and nucleosome assembly



Asf-1, CAF-1, HIRA, HJURP, and NASP are histone H3 chaperones which promote deposition of dimers of histones. H3-H4 dimers associate with histone chaperones in pre-deposition complexes (upper panel), suggesting that, like H2A and H2B, H3 and H4 are deposited as dimers in the course of de novo nucleosome formation (lower panel). Red arrows highlight the binding interface involved both in H3 dimerization and H3-ASF1 interaction. H3 variants are indicated (Polo & Almouzni, Cur Opin Genet Dev, 2006)

Histone assembly line



Schematic representation of the function of chaperones in handling histones in a chromatin assembly line, highlighting specificity for cargo, i.e., histones, and interfaces with specific partners connecting their function with particular metabolic pathways. From De Koning et al, Nat Struct Mol Biol, 2007.