Chromatin assembly and organization

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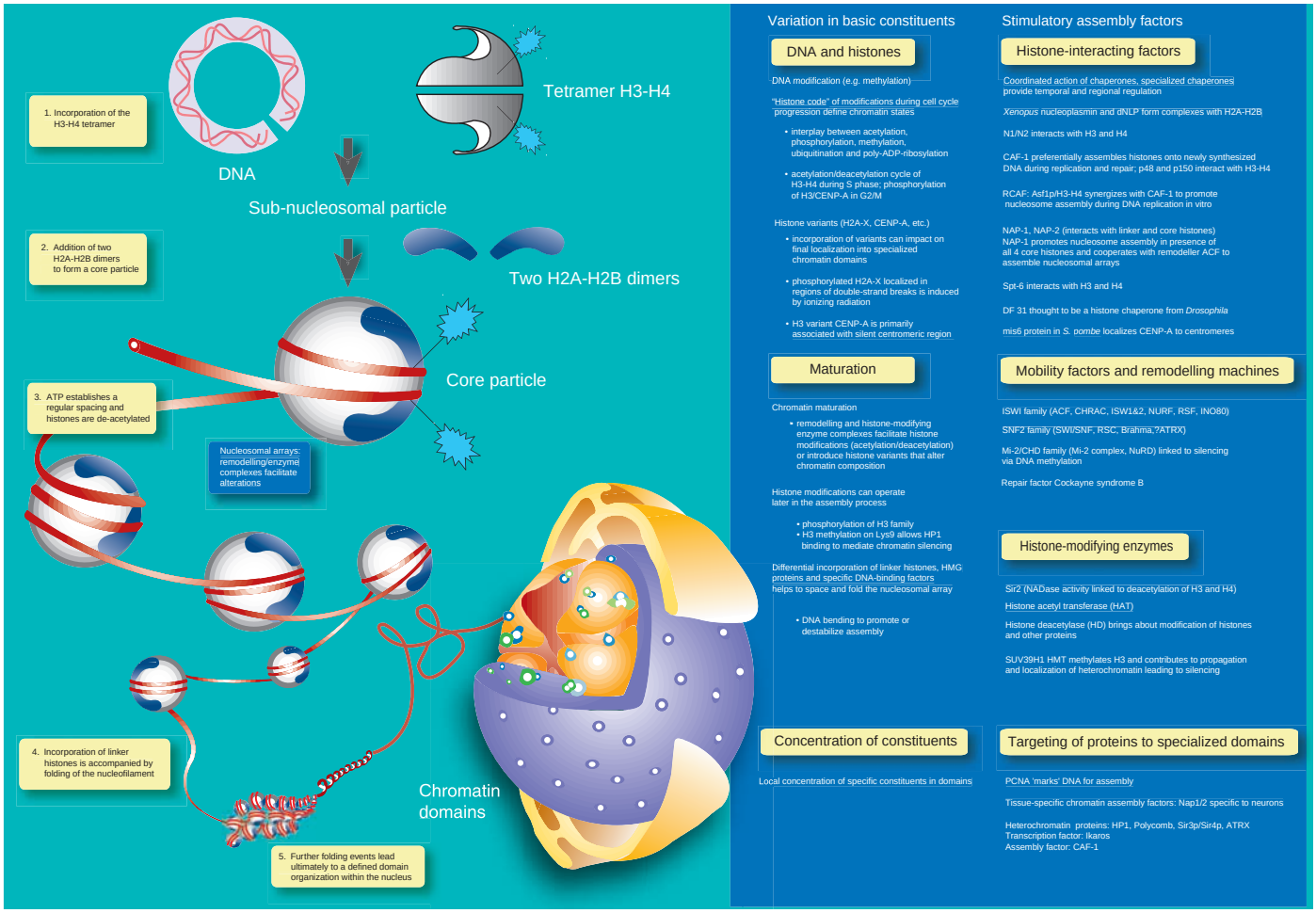
The poster shows the general steps in chromatin assembly and the diversity of chromatin organization. At each step, variation in the basic constituents of chromatin leads to the establishment of distinct final structures. The left-hand column of text provides examples of such variation; the right-hand column lists stimulatory factors that can promote progression through the assembly steps. Assembly begins with the deposition of the histone H3-H4 tetramer onto DNA, followed by the addition of two histone H2A-H2B dimers to form the core particle. The newly synthesized histones are specifically modified; typically histone H4 is acetylated at Lys5 and Lys12. During the maturation step ATP is required to establish a regular spacing, and histones are de-acetylated. The incorporation of linker histones is accompanied by folding of the nucleofilament, which is represented here as a solenoid structure containing six nucleosomes per gyre. Further folding events produce a defined organization within nuclear domains.

During the first steps of assembly, incorporation of differentially modified (e.g. methylated) DNA and histones modified in numerous ways (e.g. acetylation, phosphorylation, methylation, ubiquitination and poly-ADP-ribosylation) can produce differences in chromatin structure and activity. These modifications signal the progression of defined chromatin states, such as the acetylation/deacetylation cycle of H3-H4 during S phase or the phosphorylation patterns of H3/CENP-A in G2/M phase. The incorporation of histone variants such as H2A-X or CENP-A can also impact on the final localization of chromatin into specialized chromatin domains. More specifically, phosphorylated histone H2A-X is localized in regions of double-strand breaks induced by ionizing radiation, whereas the histone H3 variant CENP-A is primarily associated with silent centromeric regions.

In the maturation step, the differential incorporation of linker histones, HMG proteins and other specific DNA-binding factors helps to space and fold the nucleosomal array. Histone modifications can also operate at this later stage. In this context, histone H3 phosphorylation has been demonstrated to play a role in chromosome



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condensation and segregation, and methylation on Lys9 of histone H3 mediates chromatin silencing. Therefore, these early steps in assembly can have a great impact on the later steps, leading to localization of chromatin into specialized nuclear domains.

Stimulatory factors are implicated in assembly at several levels, directly binding to histones, acting as mobility/remodelling machines, functioning as histone-modifying enzymes or targeting chromatin to specialized domains.

Histone-interacting factors or chaperones may impart specificity on chromatin assembly. *Xenopus* nucleoplasmin, for example, forms complexes with histones H2A and H2B, as does *Drosophila* nucleoplasmin-like protein (dNLP). *Xenopus* N1/N2, however, interacts with histones H3 and H4. Chromatin assembly factor 1 (CAF-1) preferentially assembles nucleosomes onto newly synthesized DNA during replication and repair. RCAF promotes nucleosome assembly during DNA replication in vitro by a synergy between Asf1p/H3/H4 and CAF-1. Of the histone-interacting proteins, NAP-1 can associate with all core histones (depending on the study system), and NAP-2 interacts with both linker and core histones. Other factors include Spt-6, which interacts with histones H3 and H4, DF 31 (a putative *Drosophila* histone chaperone) and the *S. pombe* mis6 protein, which localizes CENP-A to centromeres.

Mobility factors and remodelling machines regulate DNA accessibility and are good candidates for mediators of ATP-dependent chromatin maturation. These include *Drosophila* ATP-utilizing chromatin-assembly and -modifying factor (ACF), chromatin-accessibility complex (CHRAC), nucleosome-remodelling factor (NURF) and yeast remodelling and spacing factor (RSF). Other examples are INO80, which is involved in transcription and DNA processing, SNF2 family members, and the Mi-2 complex and nucleosome-remodelling and histone-deacetylase complex (NuRD), which are linked to silencing by DNA methylation.

Histone-modifying enzymes also affect chromatin structure. Sir2, for example, has NADase activity linked to deacetylation of H3 and H4, and histone acetyltransferases (HAT) and histone deacetylases (HD) modify both histones and other interacting proteins. Significantly, the HD involved in post-replicative deacetylation is not yet identified, and several enzymes are capable of acting on the nucleosome in concert. SUV39H1 HMT, for instance, methylates H3, which has been implicated in silencing through an interaction with heterochromatin protein 1 (HP1).

The final group of stimulatory factors is targeting proteins, which may help to bring specialized proteins to specific domains in the nucleus. They might act through a 'marking' mechanism (e.g. PCNA) or by exhibiting tissue specificity (e.g. neuron-specific Nap1/2). Hypothetically, heterochromatin-associated proteins, transcription factors and assembly factors may ensure these functions and examples are given for each class. Naturally, the timing of modifications, regulatory factor expression and protein localization may provide an additional level of regulation. Detailed information on this topic can be found in a number of recent reviews (Annunziato and Hansen, 2000; Cheung et al., 2000; Mello and Almouzni, 2001; Moazed, 2001; Ridgway and Almouzni, 2000; Strahl and Allis, 2000; Wu and Grunstein, 2000).

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