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Featuring the nucleosome surface as a therapeutic target

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Chromatin is the major regulator of gene expression and genome maintenance. Proteins that bind the nucleosome, the repetitive unit of chromatin, and the histone H4 tail are critical to establishing chromatin architecture and phenotypic outcomes. Intriguingly, nucleosome-binding proteins (NBPs) and the H4 tail peptide compete for the same binding site at an acidic region on the nucleosome surface. Although the essential facts about the nucleosome were revealed 17 years ago, new insights into its atomic structure and molecular mechanisms are still emerging. Several complex nucleosome:NBP structures were recently revealed, characterizing the NBP-binding sites on the nucleosome surface. Here we discuss the potential of the nucleosome surface as a therapeutic target and the impact and development of exogenous nucleosome-binding molecules (eNBMs).

Chromatin dynamics

It remains a great challenge to fully understand how nature packs the eukaryotic genetic code into small functional chunks. The complex association of highly basic proteins and DNA to form nucleosomes is the first level of DNA compaction, followed by a cooperative nucleosome interaction to form the higher-order chromatin structure.

Since chromatin is the major regulator of gene expression and genome maintenance, it is plausible to believe that molecules that target nucleosomes have a profound impact on gene expression and genome maintenance.

We are now beginning to perceive how changes in chromatin architecture may affect gene expression. It is clear that the local chromatin state – relaxed (permissive) or condensed (repressive) – regulates the access of transcription factors, coregulators, and the basic transcription machinery to specific enhancers in target genes (reviewed in [1]). Thus, the dynamic modulation of the chromatin structure determines transcriptional and clinical phenotypic outcomes.

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Lessons from *in vitro* studies have confirmed that chromatin fibers are highly dynamic; under low-salt conditions, chromatin adopts an open conformation known as 'beads on a string' or the 10-nm fiber. In a physiological ionic environment (presence of Mg^{2+}) and the correct linker histone stoichiometry, the chromatin can fold to form a compacted chromatin structure, the 30-nm fiber [2]. Moreover, chromatin dynamics are strongly dependent on the NBP and H4 tail (the highly basic N-terminal domain of histone 4) (see Glossary) interaction with a negatively charged region on the nucleosome surface known as the acidic patch.

Here we focus on the nucleosome surface as a potential therapeutic target to regulate chromatin dynamics and a myriad of cellular disorders.

The nucleosome and its binding proteins

The nucleosome is the repetitive and fundamental unit of chromatin. NBPs are key players in modulating chromatin changes. From condensed to relaxed chromatin, NBPs may induce specific chromatin architecture modifications dependent on their unique properties (Box 1).

Glossary

Acidic patch: a negatively charged region on the nucleosome surface formed from six H2A and two H2B residues (see text).
Chromatin: a macromolecule comprising a dynamic and functional array of nucleosomes that forms the first level of organization, known as the 'beads-on-a-string' structure or euchromatin. The second level of chromatin organization is achieved when the nucleosome array folds to a highly compacted state, forming a structure known as the 30-nm fiber or heterochromatin.
Exogenous nucleosome-binding molecules (eNBMs): peptide-like molecules that bind to the acidic patch; derived from the H4 tail and chromatin-binding motifs of NBPs.
H4 tail: the N-terminal domain of histone H4 is highly basic, similar to all core histone tails. Deacetylated H4K16 tails interact with the acidic patch of adjacent nucleosomes, bringing them into a closer state and inhibiting gene expression. Acetylated H4 tails are unable to interact with the acidic patch, causing chromatin relaxation.
Linker histone: members of the histone family, linker histones (H1 and H5) do not constitute the NCP. H1 asymmetrically binds to the nucleosome and chromatin to play a crucial role in the formation of the 30-nm fiber.
Nucleosome: the fundamental unit of chromatin. The NCP comprises 145–147 bp of DNA wrapped around an octamer of four core histones (H2A, H2B, H3, and H4). The core histones have a globular domain comprising α-helices that forms the body of the nucleosome. The short N-terminal tail domains of histones are generally flexible and unstructured.
Nucleosome-binding proteins (NBPs): proteins that bind to the nucleosome, usually through the direct interaction of a NBP short motif with the acidic patch.

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Box 1. The functional side of atomically detailed NBPs

RCC1. RCC1 is a NBP that recruits the small GTPase Ran enzyme to chromatin, triggering nucleotide exchange activity. The interaction of RCC1 with the nucleosome is essential for mitosis and nuclear transport [34].
LANA. The KSHV LANA is tethered to the nucleosome, forming a minichromosome known as an episome. LANA is crucial for keeping the viral genome bound to mitotic chromosomes in a condensed chromatin state [35].
SIR3. The SIR proteins induce and hold the chromatin in a silenced state. SIR3 is a NBP with chromatin remodeler activity that, *in vitro*, is able to assemble a hypercondensed chromatin structure [36].
HMGN2. HMGN2 is a member of a broader class of HMG chromosomal proteins and plays important roles in transcription, replication, recombination, and DNA repair. The HMGN proteins bind to nucleosomes and displace linker histone H1 from the nucleosome surface. HMGN induces chromatin relaxation *in vitro* [37].
IL-33. IL-33 is a member of the IL-1 superfamily of cytokines with a fundamental role in immune modulation and inflammatory signaling. IL-33 is enriched in endothelial cells *in vivo* as a chromatin-associated factor. *In vitro*, the IL-33 chromatin-binding motif induces chromatin condensation by increasing nucleosome self-association and oligomerization [7].
CENP-C. CENP-C, a DNA-binding protein, is one of the 16 centromere proteins complexed with CENP-A, recognizing centromeric nucleosomes to maintain proper kinetochore size and a timely transition to anaphase during mitosis. This NBP is responsible for keeping the chromatin condensed [38].
PRC1. PRC1, in complex with other proteins of the Polycomb group and 'E3' ubiquitin ligase enzymes, downregulates a set of genes involved in developmental processes. PRC1 induces chromatin condensation through nonenzymatic mechanisms and probably also through enzymatic processes [39].

The first atomic structure of the nucleosome core particle (NCP), obtained by Richmond, Luger, and colleagues in 1997 [3], revealed the existence of the acidic patch, a negatively charged region formed by H2A and H2B. Later, in 2006, the first complex structure of a nucleosome:peptide was resolved, showing at atomic level that the viral peptide Kaposi's sarcoma-associated herpesvirus (KSHV) latency-associated nuclear antigen (LANA) binds to the acidic patch [4]. In the following years, another five nucleosome:NBP complex structures were published: two crystal structures (peptide:bromo-adjacent homology (BAH) domain silent information regulator (Sir) 3 [5] and protein:-regulator of chromosome condensation 1 (RCC1) [6]); one atomic structure derived from computational modeling {peptide:interleukin (IL)-33 [7]}; one from NMR imaging and modeling (peptide:high mobility group (HMG) nucleosome-binding protein (HMGN) 2 [8]); and one from a combination of crystallography, NMR, and computational modeling (peptide:centromere protein (CENP)-C [9]). These structures revealed atomic details of the interaction of NBPs with the nucleosome surface, highlighting the acidic patch as the principal protein-docking region.

Recently, a new crystallographic structure of a nucleosome:protein complex was published. Song Tan and colleagues [10] presented a structure that reveals an unexpected role for an enzyme in substrate recognition on the nucleosome, showing that a domain (Ring1B) of the enzymatic complex binds to the acidic patch. In addition, this structure reveals new binding sites for proteins on the surface of a nucleosome. A detailed NBP interaction map on the nucleosome surface is illustrated in Figure 1B,C.

The acidic patch is on target

The acidic patch, formed by six residues of H2A and two of H2B, is responsible for nucleosome–nucleosome interactions. It is a negatively charged region that forms a narrow groove on the nucleosome surface. This can be visualized on the charged surface structure of a nucleosome represented in Figure 1A. Notably, another negatively charged zone (Figure 1A) with four residues (H3: E73, I74, and D77; H4: E63) adjacent to the acidic patch provides a binding site for BAH SIR3 and Polycomb repressive complex 1 (PRC1) (Figure 1B,C) via residue D77.

In addition, the acidic patch residues Y50, V54, and Y57 on H2A create a hydrophobic pocket at the bottom of the acidic patch groove (reviewed in [11]). It is astonishing to notice that all seven nucleosome:protein complexes examined at the atomic level exploit the acidic patch as the critical region for NBP interactions. It is also remarkable that these proteins have conserved arginine residues (shown in gray in Table 1) to interact with the acidic patch.

Chromatin architecture and nucleosome-binding molecules

It has been shown that the N-terminal domain of H4 has a well-documented role in modulating chromatin architecture. When the H4 tail is acetylated or removed by proteolysis, chromatin no longer compacts as it would be expected and the chromatin structure loosens. By contrast, the deacetylated H4K16 tail interacts with the surface of adjacent nucleosome bringing them into a closer state to promote nucleosome–nucleosome interactions and form the higher-order chromatin structure (silenced chromatin, 30-nm fiber) [12].

Besides the role of acetylated H4K16 in relaxing the chromatin state, data from *Saccharomyces cerevisiae* showed that an acetylated H4K16 mark is required for the formation of both relaxed and condensed chromatin [13].

The function of the H4 tail in chromatin dynamics is still debated. However, evidence from a cryoelectron microscopy (cryo-EM) study of the chromatin fiber showed that the internucleosomal interactions between the positively charged residues of the H4 N-terminal tail and the acidic patch may account for the twist between the tetranucleosomal units, supporting the notion that H4 tail is crucial for chromatin compaction [14].

NBPs will also have major roles as chromatin structure regulators, with some NBPs inducing chromatin condensation and others favoring chromatin relaxation (Box 1 and Figure 1C).

To predict the chromatin architecture outcome on neutralizing the acidic patch we should take into account the equilibrium between NBPs and the H4 tail in acidic patch interactions. Based on binding affinity and concentration, competition for the acidic patch and other regions on the nucleosome surface will determine the final chromatin state.

Hansen and colleagues [11] have raised a beautiful hypothesis to explain the mechanism adopted by NBPs

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