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Review

Nucleosome signalling; An evolving concept☆,☆☆

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ABSTRACT

The nucleosome core particle is the first stage of DNA packaging in virtually all eukaryotes. It both organises nuclear DNA and protects it from adventitious binding of transcription factors and the consequent deregulation of gene expression. Both properties are essential to allow the genome expansion characteristic of complex eukaryotes.

The nucleosome is a flexible structure in vivo, allowing selective relaxation of its intrinsically inhibitory effects in response to external signals. Structural changes are brought about by dedicated remodelling enzymes and by posttranslational modifications of the core histones.

Histone modifications occasionally alter nucleosome structure directly, but their more usual roles are to act as receptors on the nucleosome surface that are recognised by specific protein domains. The bound proteins, in turn, affect nucleosome structure and function. This strategy enormously expands the signalling capacity of the nucleosome and its ability to influence both the initiation and elongation stages of transcription.

The enzymes responsible for placing and removing histone modifications, and the modification-binding proteins themselves, are ubiquitous, numerous and conserved amongst eukaryotes. Like the nucleosome, they date back to the earliest eukaryotes and may have played integral and essential roles in eukaryotic evolution. The present properties and epigenetic functions of the nucleosome reflect its evolutionary past and the selective pressures to which it has responded and can be better understood in this context. This article is part of a Special Issue entitled: Molecular mechanisms of histone modification function.

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1. Introduction

When the basic structure of the nucleosome was published in 1980 [10], it was a breakthrough in understanding how the vast amount of DNA in eukaryotic cells is packaged and organised (Fig. 1A). The structure explained some puzzling properties of nuclear DNA, particularly its characteristic response to nuclease digestion, and was consistent with the particles observed by electron microscopy after spreading of nuclear chromatin [17]. Indeed, the linear arrangement of nucleosomes, the "beads on a string" 10 nm fibre (Fig. 1B), provided the framework structure for higher levels of folding across interphase and mitotic chromosomes. The nucleosome also gave the four core histones a purpose in life. The histones had been known since the 1950s to be abundant, positively charged, highly conserved nuclear proteins, but prior to the discovery of the nucleosome, their function in the nucleus, was unclear. Two obvious possibilities were DNA packaging and regulation of gene expression. We now know that the nucleosome does both.

2. Histones and gene expression

Long before the discovery of the nucleosome, experiments were carried out to ask whether histones could play a role in gene expression [1]. Specifically, could purified histones bind DNA sufficiently tightly to inhibit its in vitro transcription? It was found that they could, a result that provided an important proof of principle, albeit in a highly artificial system employing a naked DNA template and bacterial RNA polymerase. The experimenters went one step further, and asked whether reducing the net positive charge of the histones, by chemical acetylation of lysines with acetic anhydride, would reduce their ability to inhibit transcription. Perhaps unsurprisingly, chemical acetylation did indeed reduce their effectiveness as inhibitors [1]. At the time of these experiments, it was known from histone sequencing that a proportion of lysines at specific positions were acetylated. In view of the in vitro findings, could acetylation be involved in moderating the histones' ability to influence transcription in vivo? With the advent of the nucleosome, it became possible to assess the relevance of these in vitro findings to processes within the nucleus itself, a subject to which we return later.

Thus, from the beginning, the nucleosome was more than just a DNA packaging device. Despite the fact that the associated DNA is wrapped around the outside of the nucleosome, the interactions have sufficient strength to prevent most DNA binding proteins from effectively accessing their binding sequences. This has been confirmed experimentally (for example [27] and the references therein), leading to the view

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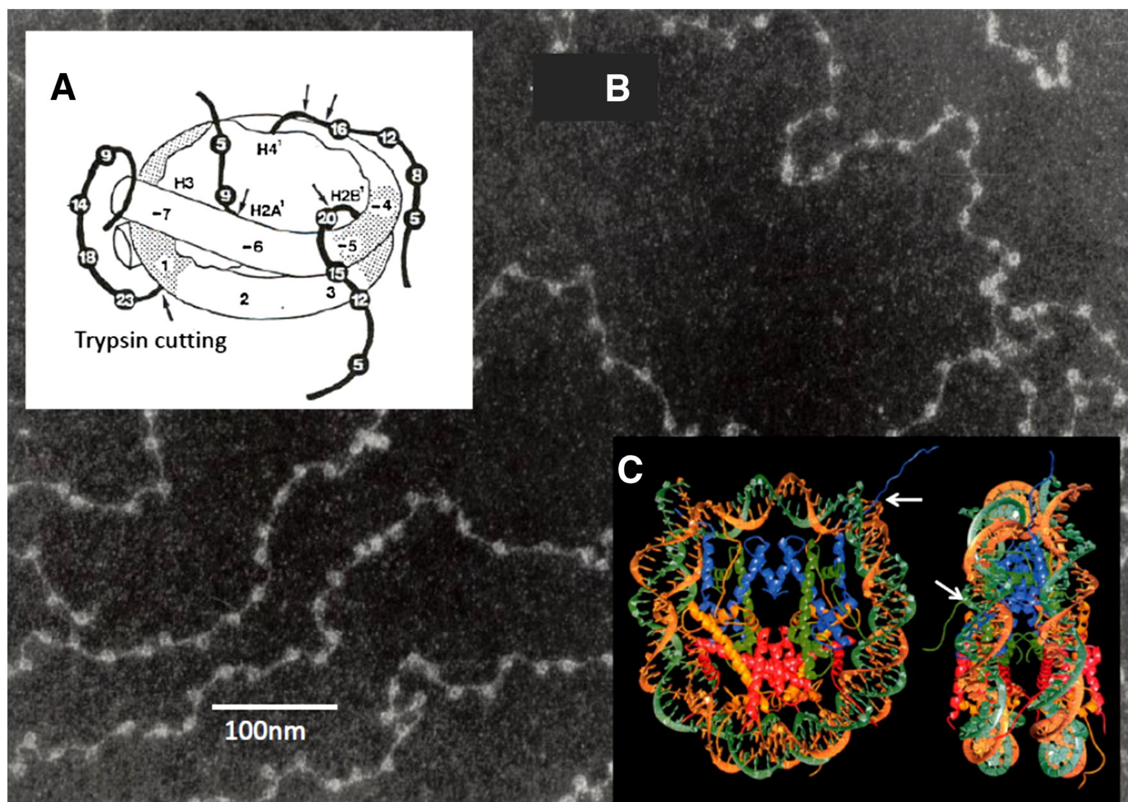

Q2 **Fig. 1.** *Nucleosome structure.* A. A drawing of the nucleosome core particle based on X-ray crystallography, nuclease digestion and histone cross-linking [10]. The core comprises eight histones (two each of H2A, H2B, H3 and H4), around which are wrapped 147 bp of DNA in 1 3/4 left-handed, superhelical turns. The numbers $\pm$1–7 indicate complete 10 bp turns along the DNA strand, progressing in either direction from the dyad axis (left side). The N-terminal tail of one of each of the core histones is shown and lysines that can be modified by acetylation are numbered. The tails can be removed by proteolysis (trypsin) and cutting sites are indicated by arrows. The sites at which the tails emerge from the DNA are accurate (based on later information), as are their overall lengths, but their structures are flexible and variable. B. The background to panels A and C is a dark-field electron micrograph showing nucleosomes and linker DNA in the beads on a string configuration, the 10 nm fibre. Chicken erythrocyte nuclei were lysed in dilute salt solution. Released chromatin was fixed with formaldehyde, spread onto carbon coated grids by centrifugation and stained with uranyl acetate [17]. The image was provided by Donald and Ada Olins. C. Computer generated ribbon diagram showing the structure of the nucleosome core particle based on X-ray crystallography at 2.8 Å resolution. The dyad axis is at the top. The sugar-phospate backbones of the complementary strands of the DNA helix are traced in brown and green and the base pairs shown as lines of corresponding colour. The main chains of the core histones are shown in yellow (H2A), red (H2B), blue (H3) and green (H4). Coiled regions are α helices. The points at which one of the N-terminal tails of H3 (upper) and H4 (lower) exits the DNA are indicated by arrows. The tails are mostly (not entirely) unstructured in crystals, preventing accurate visualisation.
Images are from [13].

that the nucleosome's effect on gene expression is essentially inhibitory. It is a structure that must be moved aside, or at least partly unravelled, to allow both binding of regulatory proteins and transit of polymerases. We now know that these manoeuvres can be achieved in vivo by families of chromatin remodelling enzymes [19]. At first sight, the task of these enzymes is likely to be made easier by reducing the net positive charge of the core histones through lysine acetylation. However, with more detailed understanding of nucleosome structure came the realisation that the amino acids primarily responsible for the binding and configuration of nucleosomal DNA were located across the globular histone core regions, while the great majority of those susceptible to in vivo acetylation were located on the histone N-terminal tails, unstructured regions located outside the DNA (Fig. 1A, C) [12,14]. The tail domains are not essential for forming the nucleosome itself, though they can influence its fine structure [16]. They play a role in the formation of higher order chromatin structures, probably by mediating inter-nucleosomal interactions [9,14]. It has become apparent that these interactions are complex. Individual tails have different functions that are interdependent and modifiable by acetylation status in ways that both enhance and suppress chromatin folding (reviewed in [18]).

3. The nucleosome allows genome enlargement

The operon model in which activator and repressor proteins bind to specific DNA sequences is still the paradigm on which our models of gene regulation are based. The paradigm works well for small genomes, but encounters problems when confronted with the large genomes common in multicellular eukaryotes. As organisms have increased in complexity through evolutionary time, genome size has increased beyond the relatively modest increase in gene number. For example, the bacterium *Escherichia coli* has 4200 genes in 4.5×10^6 bp of DNA (~1.1 Kb/gene) while *Homo sapiens* has ~24,000 genes in 3.3×10^9 bp Q4 of DNA (~140 Kb/gene). The reasons for this excess of non-coding DNA in higher eukaryotes remain uncertain, but it certainly makes mechanisms of gene regulation based solely on transcription factor (TF) binding untenable. Most eukaryotic TF binding sequences have remained relatively short at around 6–8 bp [33] and a typical 6 bp consensus TF binding sequence will occur in the human genome, by chance alone, once every 4096 (4^6) base pairs, or about 700,000 times. Even a relatively large binding sequence of 10 bp would still occur about 3000 times. As most TFs can bind variants of their consensus sequences, the number of potential binding sites will be even higher. Thus, eukaryotes have had to develop processes that not only package and organise an increasing amount of DNA, but also restrict access of DNA binding proteins only to those genomic regions at which they are required.

One way of addressing this issue is to keep key regulatory regions free of nucleosomes and thereby accessible to TFs, whereas other regions are nucleosomal and inaccessible. Regions of low nucleosome density revealed by hypersensitivity to nuclease digestion (DNAse Hypersensitive Sites, DHS), have been known for many years and tend

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