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Phil. Trans. R. Soc. Lond. B 1978 **283**, 291-293
doi: 10.1098/rstb.1978.0026

Phil. Trans. R. Soc. Lond. B. **283**, 291–293 (1978) [291]
Printed in Great Britain

Histone interactions, histone modifications and chromatin structure

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A subunit structure for chromatin is now well established (Hewish & Burgoyne 1973; Burgoyne, Hewish & Hobbs 1974; Olins & Olins 1973, 1974; Woodcock 1973; Rill & Van Holde 1973; Kornberg 1974; Baldwin, Boseley, Bradbury & Ibel 1975; Oudet, Gross-Bellard & Chambon 1975). Nuclease digestion of chromatin gives a series of well defined products consisting of monomers, dimers, trimers and higher oligomers (Hewish & Burgoyne 1973; Burgoyne *et al.* 1974; Noll 1974*a*, *b*). There are two types of monomer subunit; the subunit containing the full DNA repeat lengths of about 200 base pairs as found in most tissues and called the nucleosome which, on further digestion, yields a well defined subnucleosome 'core' particle containing 140 base pairs of DNA (Van Holde & Isenberg 1975). Both monomer particles are thought to contain eight 'nucleosomal' histones (H2A, H2B, H3 and $H4)_2$ (Kornberg 1974). The very lysine rich histone H1 is not required for the integrity of the chromatin subunit (Bradbury *et al.* 1972*b*; Shaw *et al.* 1976) and it is generally accepted that H1 is involved in maintaining and generating higher order chromatin structures.

Neutron scatter studies of the monomer nucleosomes (Bradbury *et al.* 1975; Hjelm *et al.* 1977) and 'core' particles (Pardon *et al.* 1975; Suau, Kneale, Baldwin & Bradbury 1977) fully support a model (Kornberg 1974; Baldwin *et al.* 1975) in which DNA is wrapped around a core of histones. The overall diameter of the particle is approximately 10.2 nm (Bradbury *et al.* 1975). The properties and interactions of histones are entirely consistent with such a model. Nuclear magnetic resonance studies of histones and large histone fragments show that the histone complexes $(H3)_2(H4)_2$ (Moss, Crane-Robinson & Bradbury 1976*b*) and (H2A) (H2B) (Moss *et al.* 1976*a*) are held together by interactions between structured apolar central and carboxyl regions; 31–95 of H2A, 37–114 of H2B in the (H2A, H2B) dimer and 42–135 of H3, 37–102 of H4 in the $(H3)_2(H4)_2$ tetramer (Bohm *et al.* 1977). These structured apolar regions of the histones are thought to comprise the protein core of the nucleosome (Baldwin *et al.* 1975). The very basic N-terminal regions are not involved in histone complex formation and are major sites of interaction with DNA. In the nucleosome model these basic regions are complexed with DNA on the outside of the apolar protein core.

There is evidence to suggest that the next order of chromatin structure is a coil of nucleosomes (Carpenter, Baldwin, Bradbury & Ibel 1976; Finch & Klug 1976). Neutron diffraction and electron microscopy studies on chromatin are consistent with (but do not prove) a coil with pitch of about 10 nm containing about 6 nucleosomes per turn. The coil has the crude dimensions of 30 nm diameter with a hole 10 nm diameter along the axis. Neutron diffraction results from fibres of H1 depleted chromatin (Carpenter *et al.* 1976) are also consistent with a coil which implies that histone H1 is not essential to the coiling of a string of nucleosomes at the very high concentrations found in chromatin fibres. One of the functions of H1 may be to stabilize this coil while other functions involve the generation of higher order chromosome structures. A multifunctional rôle of H1 is consistent with its molecular properties. H1, which

contains 216 residues, is almost twice as large as the other histones and has three distinct regions called the nose, head and tail. The nose (residues 1–41) has a very basic segment from 19–35, the head (residues 41–123) can be precisely folded into a globular structure, while the tail (residues 123–216) is very basic and contains in excess of 80% lysine, proline and alanine (Jones, Rall & Cole 1974). R. D. Cole has found that these three regions are conserved to differing degrees with the globular head being the most strongly conserved. H1 has been cleaved into each of these well defined regions and into the halves 1–123 and 124–216 (Chapman, Hartman & Bradbury 1976). The C-terminal basic half 124–216 binds strongly to DNA and generates a behaviour similar to the salt-induced contraction of chromatin. The N-terminal half binds only weakly to DNA. This suggests that the basic C-terminal tail is the strong binding region to DNA while the head and nose regions are required for other functions.

An attractive current hypothesis is that the different conformational states of chromosomes through the cell cycle are determined by postsynthetic modifications of histones (Allfrey, Faulkner & Mirsky 1974; Pogo, Allfrey & Mirsky 1966; Langan 1969; Sung & Dixon 1970; Bradbury *et al.* 1972*a*, 1973, 1974; Louie, Candido & Dixon 1974). In view of the high degree of conservation of the sequences of histones it is thought highly significant that histones are subjected to modification which radically alter the nature of the modified residues. Of the different modifications so far reported, two reversible modifications are of considerable interest: acetylation of lysines in the nucleosomal histones and phosphorylation of serines and threonines in H1. Without exception all *in vivo* histone modifications so far observed are located in the well defined basic histone segments implicated as major DNA binding sites and are thus thought to modulate the histone–DNA interactions. The acetylation sites of lysines in the nucleosomal histone found by G. H. Dixon are H2A (5) H2B (5, 12, 15, 20), H3 (9, 14, 18, 23) and H4 (5, 8, 12, 16) and in the tetraacetylated states the basic change density of the N-terminal regions is considerably reduced. It has been proposed therefore that histone acetylation is a mechanism by which DNA in nucleosomes is made available for DNA replication (Dixon) and transcription (Allfrey).

The other major cell-cycle dependent histone modification, phosphorylation of H1, has been strongly implicated in the overall control of chromosome structure and in particular in the process of chromosome condensations leading to metaphase chromosomes (Bradbury *et al.* 1972*a*, 1973, 1974). In the highly synchronous nuclear division cycle of *Physarum polycephalum*, H1 undergoes rapid phosphorylation in mid and late G2 when the chromosomes are observed to be condensing. Similar results have been reported with synchronized mammalian cells and in plant cells. The activity of histone phosphokinase also varies cyclically, being low early in the cycle and increasing rapidly to a maximum which precedes the maximum uptake of phosphate by H1. More recently it has been found that at least two enzymes are involved in this activity, one specific for H1 and the other a more general phosphokinase (Hardie, Matthews & Bradbury 1976). The activities of both enzymes vary cyclically but with slightly different cell cycle dependencies. The location and properties of H1, the cyclical variation of H1 phosphorylation which is driven by a cyclical variation in histone phosphokinase and the physical properties of phosphorylated H1 all support the proposal that H1 phosphorylations form an important series of events in the overall control of chromosome structure and of chromosome condensation into the metaphase chromosomes.

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