Holding it together: chromatin in the Archaea

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Recently, several advances have been made in the understanding of the form and function of archaeal chromatin. Remarkable parallels can be drawn between the structure and modification of chromatin components in the archaeal and the eukaryotic domains of life. Indeed, it now appears that key components of the hugely complex eukaryotic chromatin regulatory machinery were established before the divergence of the archaeal and eukaryotic lineages.

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It is a universal requirement of living organisms that they compact their genomic DNA so it can fit into cells. Bacterial and archaeal cells of ~1 μm in diameter must accommodate ~1 mm of DNA, and the task facing higher eukaryotic cells is even more daunting – they must compress 2 metres of DNA into a nucleus of 10 μm diameter. Thus, in eukaryotic cells, the systematic control of chromatin modulation is an integral component of the essential nuclear processes of transcription, DNA replication and DNA repair [1]. In this article, we will discuss recent developments in the study of archaeal chromatin compaction systems, in particular focusing on the close evolutionary relatedness between Archaea and Eukaryotes.

The most widely accepted version of three-domain model for the evolution of cellular life indicates that the last common ancestors of the archaeal and eukaryotic domains existed during a period of evolutionary history following the divergence of the Bacteria [2] (Fig. 1). Genomic and biochemical analyses have revealed that the core machineries for transcription and DNA replication were established in the common ancestors of Archaea and Eukaryotes, and therefore are fundamentally related in present-day Archaea and Eukaryotes.

During the evolution of the archaeal domain of life a further bifurcation occurred, yielding two archaeal subdomains, the Crenarchaeota and Euryarchaeota (Fig. 1). In this article, we will focus on studies performed in members of the genus *Sulfolobus*, which are hyperthermophilic organisms of the Crenarchaeota, and also in several methanogenic Archaea of the Euryarchaeota. As discussed below, it appears that these various Archaea use different subsets of DNA-binding proteins to achieve DNA compaction (Table 1).

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Eukaryotic and bacterial DNA compaction

The primary unit of DNA compaction in eukaryotic nuclei is the nucleosome. This contains an octamer of histone proteins: two copies each of H2A, H2B, H3 and H4. In the assembly of the nucleosome, two H3–H4 dimers interact to form a tetrameric complex. This can bind DNA, generating the 'tetrasome' structure (see below). Two H2A–H2B dimers bind to opposite sides of the H3–H4 tetramer to form the full octamer. The octamer wraps ~150 bp of DNA in two left-handed solenoidal coils. The nucleosome is generally repressive to nuclear processes such as transcription, and eukaryotic cells have evolved mechanisms to overcome this effect. Modulation of chromatin is brought about by two mechanisms. First, cells possess ATP-utilizing complexes that physically reposition or 're-model' nucleosomes [3]. Second, the histone proteins contain N- and C-terminal tails. The N-terminal tails are thought to be important for mediating internucleosome interactions and are the sites of extensive posttranslational covalent modification [1]. Modification of histone tails by acetylation and methylation is a key event in the regulation of eukaryotic nuclear processes [1,4].

In contrast to the complex regulatory circuits modulating eukaryotic chromatin, compaction of bacterial DNA appears to be far simpler. Bacteria possess a range of small basic proteins, such as HU and FIS, that compact DNA to varying degrees. Although bacteria can use these proteins as transcriptional co-activators and co-repressors (e.g. HU serves as a co-repressor for the *gal* operon in *Escherichia coli* [5]), it does not appear that bacteria specifically modulate their chromatin proteins by posttranslational modification.

Archaeal histones

In 1990, a striking discovery was made by John Reeve's laboratory, namely that a methanogenic archaeon, *Methanothermus fervidus*, contained a homologue of eukaryotic histones. Similar to eukaryotic histones, the archaeal histones can compact DNA and accelerate the mobility of DNA in gel-shift assays [6]. Subsequent work from Reeve and others has revealed that many of the Euryarchaeota, but none of the Crenarchaeota sequenced to date, possess histones, and in many species more than one histone orthologue is encoded (Table 1). In general, the archaeal histones are shorter than eukaryotic histones, corresponding to the core histone fold, and lacking the N- and C-terminal tail extensions (Fig. 2a). The eukaryotic histone tails are sites of extensive regulatory posttranslational modification and, therefore, are of considerable importance in the

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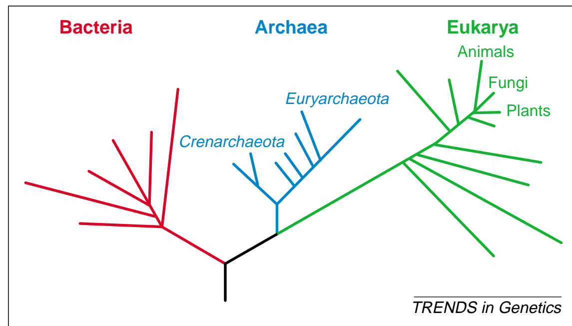

Fig. 1. The universal phylogenetic tree derived from comparative analyses of rRNA sequences. Reproduced with permission from [50].

regulation of the compaction and accessibility of nucleosomes [1]. As discussed below, the absence of the tails in archaeal histones could have ramifications both for DNA binding and regulatory processes. Biochemical analyses revealed that in the absence of DNA the archaeal histones form stable dimers. Dimerization is not limited to homodimerization; in archaeal species with more than one histone homologue, heterodimerization can occur [7]. As different histone homologues can have different DNA-binding properties, varying the relative expression of histone homologues provides the potential to modulate the degree of chromatin compaction. An example of this has been described for *M. fervidus*. This organism encodes two histone homologues, HMfA and HMfB, and it has been observed that the relative abundance of these proteins varies with the growth phase of a culture [7]. Specifically, the level of HMfB was seen to increase as cells approached stationary phase. As HMfB compacts DNA more extensively than does HmfA, this led to the proposal that the elevated HMfB level is a component of the adaptation of cells for limited genome expression and replication in stationary phase [7].

Table 1. Distribution of abundant DNA-binding proteins and candidate chromatin modifying enzymes in archaeal species

Species[a]	Histones	Alba	Sir2	Other[b]	Growth temp. (°C)
Methanopyrus kandleri	4[c]	2	1	7kMk	100
Pyrococcus furiosus	2	1	1		100
Pyrococcus horikoshii	2	1	1		100
Pyrococcus abyssi	2	1	1		100
Aeropyrum pernix	**0**	**2**	**1**		**95**
Pyrobaculum aerophilum	**0**	**1**	**1**		**95**
Methanococcus jannaschii	5	1	0		85
Archaeoglobus fulgidus	2	2	2		85
Sulfolobus solfataricus	**0**	**2**	**1**	**Sso7 (3)**	**80**
Sulfolobus tokodaii	**0**	**2**	**1**	**Sso7 (2)**	**80**
Methanobacterium thermoautotrophicum	3	1	0		70
Thermoplasma acidophilum	0	1	0	HU	60
Thermoplasma volcanium	0	1	0	HU	60
Ferroplasma acidarmanus	0	1	0	HU	40
Methanosarcina barkeri	1	0	0	MC1	<40
Methanosarcina acetivorans	1	0	0	MC1 (2)	<40
Methanosarcina mazei	1	0	0	MC1 (2)	<40
Halobacterium	4[d]	0	0	MC1	<40

[a]Crenarchaeal species are highlighted in bold.
[b]Figures in parenthesis indicate number of genes encoding this protein in genome.
[c]Two polypeptides with single histone folds plus one polypeptide with two histone folds.
[d]Two polypeptides with two histone folds each.

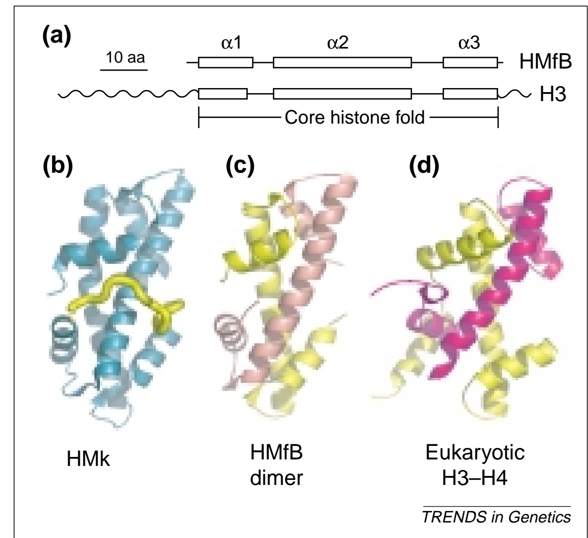

Fig. 2. Structures of archaeal and eukaryotic histones. (a) Linear representation of secondary structural elements of archaeal histone HMfB and eukaryotic histone H3. Alpha helices are depicted as open boxes and marked as α1, 2 and 3 and the N- and C-terminal tails of H3 shown by wavy lines. (b–d) A comparison of crystal structures of (b) HMk, (c) $(HMfB)_2$ and (d) H3–H4 dimer. In the H3–H4 dimer, H3 is coloured yellow and H4 is pink. The linker region between the two histone folds in HMk is highlighted in yellow. The figures were generated using the PyMol software package (http://pymol.sourceforge.net/) using the coordinates deposited in the Protein Data Bank (Accession numbers 1F1E, 1BFM and 1AOI respectively).

A particularly intriguing histone homologue has been identified in *Methanopyrus kandleri*. This molecule (HMk, also called MKaH) contains two predicted histone folds separated by a short linker region [8]. Recent structural studies have revealed that the two histone folds within a single monomer interact to produce a pseudo-dimer (Fig. 2b). These pseudo-dimers themselves dimerize to produce a pseudo-tetramer, structurally similar to the eukaryotic $[H3–H4]_2$ tetramer [9].

In addition to HMk, structural studies have been performed on the more conventional histones, HMfA and HMfB from *M. fervidus* [10]. These have confirmed the sequence homology and revealed that the euryarchaeal histones do indeed possess the classical histone fold and that they can dimerize to produce a structure akin to the eukaryotic H3–H4 dimer (Fig. 2c,d). The dimers must assemble into tetramers to bind DNA. This dimer–dimer interface is formed by a four-helix bundle (4HB) in eukaryotic nucleosome structures [11]. Thus, an archaeal nucleosome contains a tetramer of protein analogous to the eukaryotic $[H3–H4]_2$ tetrasome. In agreement with the absence of archaeal homologues of histones H2A and H2B, no evidence has been obtained for archaeal histone octamers. Furthermore, nuclease digestion patterns of archaeal nucleosomes and eukaryotic tetrasomes are strikingly similar [12,13]. In Archaea, mutagenesis of residues

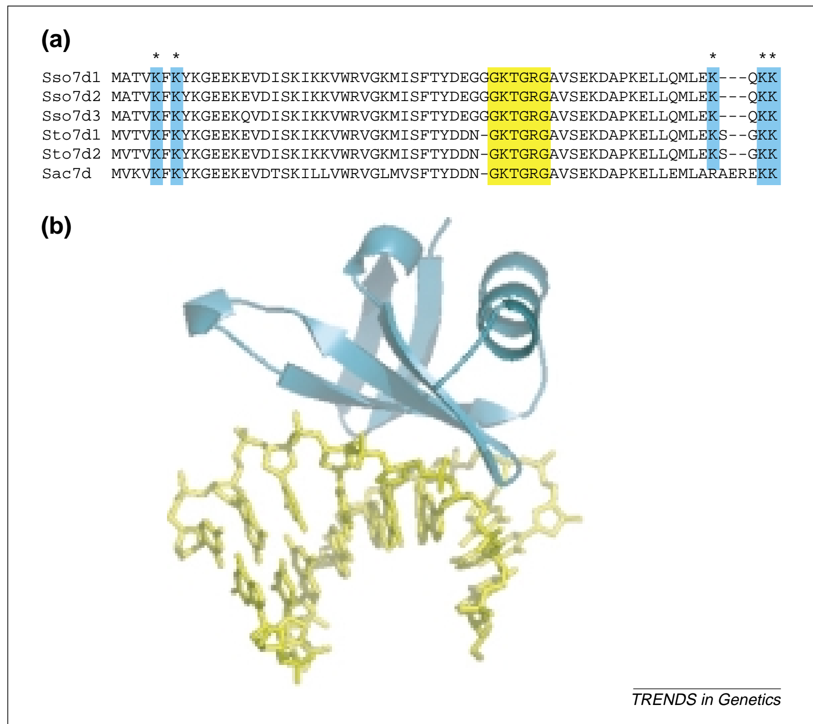

Fig. 3. Structure and sequence of Sul7d family members. (a) Sequence alignment of Sul7d homologues. The candidate ATP-binding motif is highlighted in yellow and lysines methylated *in vivo* are indicated by asterisks and highlighted in blue. (b) Structure of Sul7d bound to DNA. The duplex is kinked by 70° due to interactions in the minor groove. The figures were generated using the PyMol software package using the coordinates deposited in the Protein Data Bank (Accession number 1AZP).

within the predicted 4HB has revealed the importance of this region for stabilization of the tetramer and thus DNA binding [14]. Additionally, this interface is important in governing the direction of supercoiling by archaeal histones [15]. Initial studies carried out under low salt conditions and at low temperature indicated that an archaeal histone tetramer caused positive supercoiling of DNA [16]. However, the direction of the superhelicity produced by archaeal histones is dependent upon salt and temperature conditions, and, at physiological temperatures and salt concentrations, negative supercoils are constrained [17]. Subsequent work revealed that eukaryotic $[H3–H4]_2$ tetramers could also constrain positive supercoils and revealed that modification of the H3–H3 interface could influence the ability of tetramers to do so [18,19]. In agreement with this, a recent study by Reeve and colleagues found that mutation of certain key residues within the dimer–dimer interface also altered the directionality of supercoiling imposed by archaeal histone tetramers [15].

This supports a model in which structural flexibility within the dimer–dimer interface modulates the handedness of supercoiling, this flexibility being dictated by the component histones. In this light, it is intriguing to note that under a wide variety of conditions the covalently constrained HMk pseudodimer has only been observed to induce negative supercoiling. This could be due to limitations to the number of structural conformers that can be adopted by this unusually constrained molecule.

The presence of up to five histone homologues in some archaeal species leads to the possibility of a wide range of tetramers being formed, each of which might have preferred conformations and DNA-binding selectivities. Clear comparisons can drawn between the presence of multiple archaeal histones and the existence of histone variants in higher Eukaryotes, and it is likely that the rules being elucidated for the consequences of heteromerization of archaeal histones can be extrapolated to their eukaryotic homologues.

Chromatin in the crenarchaeote *Sulfolobus* species

Members of the *Sulfolobus* genus do not have histones; instead two highly abundant DNA-binding proteins have been characterized. The first, typified by Sso7d of *Sulfolobus solfataricus*, is a 7-kDa monomeric DNA-binding protein. Its distribution is limited to *Sulfolobus* species, but it is highly expressed and highly conserved in all three species for which we have sequence information. *S. solfataricus* has three different genes encoding Sso7d and *Sulfolobus tokodaii* has two, all of which share >90% sequence identity (Fig. 3). Because of the presence of several genes encoding Sso7d and because it has been traditionally named according to the organism from which it was isolated (e.g. Sso7d from *S. solfataricus*, Sac7d from *S. acidocaldarius*), we propose a generic family name for this protein of Sul7d (for *Sulfolobus* 7-kDa DNA-binding protein). Sul7d makes up ~5% of total soluble cellular protein [20], and binds DNA non-cooperatively with a dissociation constant in the range 1–5 μM and a footprint of ~4 bp [21]. Sul7d interacts with duplex DNA primarily in the minor groove, intercalating two hydrophobic residues, introducing a sharp kink and unwinding the duplex [22]. DNA complexed with Sul7d has an increase in melting temperature of up to 40°C [21], and it has been postulated that Sul7d can sheath duplex DNA with a protein coat [23]. Recently it has been suggested that Sul7d compacts relaxed or positively supercoiled DNA and could therefore have a role in DNA packaging *in vivo*, perhaps in combination with other DNA-binding proteins such as Alba [24] (see below).

Native Sul7d displays heterogeneous methylation of up to five lysine residues [20]. Lysine methylation has been very much in vogue since it was realized that methylation of histones is an important mechanism for chromatin regulation [4]. The significance in the case of Sul7d provides one of the first enigmas attached to this protein. The methylation does not alter the DNA-binding affinity of the protein, and is found to increase after heat shock [25]. At present we do not know the identity of the methylase for Sul7d. The majority of eukaryotic lysine methyl transferases contain SET domains [4,26]. However, no SET-domain proteins are found in Archaea. It is likely therefore that a novel class of lysine methyltransferases exists in Archaea. Lysine methylation has also been noted in other proteins in *Sulfolobus*, such as β-glycosidase and glutamate

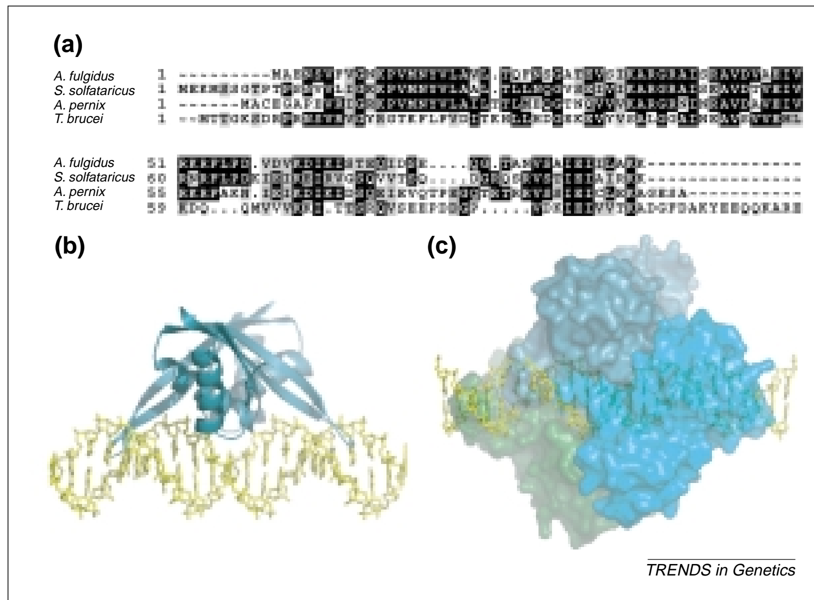

Fig. 4. Structure and sequence of Alba. (a) Sequence alignment of three archaeal Alba homologues, from the crenarchaeotes *Sulfolobus solfataricus*, *Aeropyrum pernix* and the euryarchaeote, *Archaeoglobus fulgidus*) and one Eukaryote (*Trypanosoma brucei*). Sequence identity is highlighted in black and similarity highlighted in gray. (b) Model of a dimer of Alba bound to DNA (PDB accession number 1H0X). The β-hairpin arms interact with the minor groove, and the body of the dimer contacts the central major groove. The degree of distortion of the DNA in the complex is unknown. (c) Model of three dimers of Alba bound consecutively to a DNA duplex. The dimers are rotated by 120° with respect to one another, and overlap along the DNA surface to coat the nucleic acid extensively.

dehydrogenase, and accordingly might be a generalized cellular response to heat shock.

The last enigma attached to Sul7d concerns the enzymatic activities that could be associated with the protein. Sul7d was originally thought to have RNase activity, however this has now been discounted conclusively (reviewed in [20]). It has been proposed that Sul7d has a conserved ATP-binding motif (GXXGXG) and can hydrolyse ATP. This activity is linked to an ability to renature and disaggregate proteins denatured by high temperature [27], suggesting a possible role as a chaperone analogous to the heat shock proteins. The Sul7d fold is related to that of the eukaryotic chromodomain, which mediates protein–protein interactions in proteins targeted to chromatin [28]. It is particularly intriguing that Sul7d is methylated at lysine residues and chromodomains are specific methyl-lysine recognition modules [29]. It is possible therefore that the methylation of Sul7d could facilitate multimerization of the protein. A second implication from this evolutionary relationship is that the chromodomain might have been an ancient general protein-binding chaperone fold that in Eukaryotes has become specialized to only recognize modified lysines.

Thus, in Sul7d we have a small protein (little more than a polypeptide) that comes with several mysteries attached. It is both conserved and abundant, suggesting a fundamental role, and yet unique to the *Sulfolobales*. It binds and introduces structural distortion into DNA, suggesting a role in chromatin structure, and yet can act as an ATP-dependent chaperone. Finally, it is modified by methylation and shares a fold with the eukaryotic chromodomain family. Clearly, there is still a deal of work to be done if we are to understand the significance and function of this enigmatic protein.

Alba

A second abundant non-sequence-specific DNA-binding protein has been characterized in *Sulfolobus*. This protein, Alba (also known as Ssh10b, Sso10b and Sac10b, depending on species of origin), is found not only in *Sulfolobus*, but also in many other Archaea and some Eukaryotes [30,31]. Within the Archaea, Alba appears to be restricted to the thermophiles and hyperthermophiles (Table 1). Interestingly, wherever Alba is present, a second chromatin protein is also encoded: a histone, Sul7d or a homologue of bacterial HU. Similarly, archaeal species lacking Alba seem to encode histones plus another DNA-binding protein, such as MC1 in the mesophilic methanogens (Table 1). Whether there is any interaction or co-operation in chromatin formation by these different molecules is currently unknown. It is tempting to speculate that Archaea require more than one type of chromatin protein to compact DNA fully.

In solution, Alba exists as a homodimer, and has been observed to induce negative supercoiling of DNA [32]. Furthermore, an electron micrographic study has revealed that Alba coats dsDNA without significant compaction, protecting the nucleic acid from digestion by nucleases [33]. Recent structural studies have revealed that Alba has a mixed α/β fold reminiscent of the C-terminal domain of bacterial translation initiation factor IF3 and the N-terminal domain of the nuclease DNaseI [34] (Fig. 4). A long β-hairpin arm formed by two of the β-strands extends from the body of the protein. In the dimeric structure, these arms extend in opposite directions and span a distance of ~40 Å. The central body of the Alba dimer has a highly basic surface that includes two highly conserved loops separated by ~20 Å – approximately the width of the DNA double helix. These loops contain two consecutive lysine residues (Lys16 and Lys17) that are both implicated in DNA binding. Lys16 is the site of acetylation in *Sulfolobus* that is known to modulate the DNA-binding affinity of the protein [34] (see below). The Alba dimer can be docked onto a DNA duplex, bringing the two extended arms into contact with equivalent minor groove regions and allowing the central body containing the two lysine residues to contact the major groove (Fig. 4). At present, it is unclear how much distortion of the DNA occurs on binding by Alba. The model allows consecutive dimers of the Alba protein (related by rotation through 120°) to overlap along the DNA duplex, giving rise to a densely coated nucleoprotein filament, with virtually complete coating of the nucleic acid by the protein. This model is supported by a variety of data that suggest Alba coats DNA completely, rendering it resistant to nucleases, but does not significantly compact the DNA [33].

Other euryarchaeal chromatin proteins

Another abundant chromatin protein, MC1, has been identified in some methanogenic Archaea (see Table 1). This 93-residue protein binds preferentially to negatively supercoiled DNA in a non-cooperative manner [35,36]. Binding causes considerable distortion to DNA and results in compaction of relaxed circular molecules [37,38]. Intriguingly, *Thermoplasma acidophilum* encodes a homologue of bacterial chromatin protein HU, which helps to protect DNA from thermal denaturation [39]. Finally, in *Methanopyrus kandleri,* in addition to HMk, the histone homologue described above, a second abundant DNA-binding protein, 7kMk, has been identified. This homodimeric protein binds and bends DNA, and can constrain negative supercoils [40].

Interactions between archaeal chromatin and DNA metabolic processes

In Eukaryotes, the regulation of chromatin by physical and covalent modification of core histones is an integral aspect of DNA metabolic processes such as transcription, DNA repair and replication [1]. In this section, we will focus on studies investigating the effect of archaeal chromatin proteins on transcription. We shall only briefly introduce the archaeal basal transcription machinery, as it has been reviewed recently elsewhere [41]. The archaeal RNA polymerase (RNAP) is similar in subunit composition and sequence to eukaryotic RNAP II. Like RNAP II, archaeal RNAP requires general transcription factors for efficient promoter recognition; these have been identified as homologues of eukaryotic TATA-box binding protein (TBP) and TFIIB (termed TFB in Archaea) [41].

Eukaryotic nucleosomes are generally repressive to transcription. This innate repression can be partially alleviated by covalent modification of histone tails or, *in vitro*, by removal of the tails [1,42]. Furthermore, recent work shows that passage of RNAP II through a nucleosome displaces one H2A–H2B dimer [43]. The absence from Archaea of histone tails, H2A and H2B might suggest that the archaeal histone tetramers could be less of a barrier to transcription than eukaryotic nucleosomes. However, work by Luse and colleagues has revealed that eukaryotic $[H3–H4]_2$ tetrasomes are almost as strong a block to RNAP II transcriptional elongation as are octamers [44]. Furthermore, archaeal nucleosomes have been demonstrated to be generally repressive to *in vitro* transcription, although it is not currently known which stage(s) in the transcription process is blocked [45]. It is an intriguing possibility that Archaea, like Eukaryotes, could possess machinery to overcome this repressive effect. Although lacking the N-terminal tails of eukaryotic histones and apparently not possessing any covalent modification *in vivo*, there is the potential for differential gene expression to be mediated by archaeal histones. This could be effected by varying expression levels of individual histones, such as described above for HMfA and HMfB, resulting in tetramers of varying composition and consequent DNA-binding properties [7].

Sulfolobus Sul7d binds, bends and compacts DNA *in vitro.* This protein has been observed to inhibit the positive supercoiling activity of reverse gyrase [24]. However, Sul7d also has a stimulatory effect on *in vitro* Holliday junction resolution by the *Sulfolobus* junction-resolving enzyme, Hjc [46]. In both cases this effect could be due to steric hindrance imposed by Sul7d binding DNA. In the case of reverse gyrase, this would inhibit access to DNA, in the case of Hjc, it has been proposed that Sul7d prevents formation of inhibitory higher-order complexes on junction arms, but does not affect junction binding by the resolvase [24,46].

Sul7d had no effect on a reconstituted *in vitro* transcription reaction at concentrations of up to 300 μM [31]. However, recombinant Alba protein was found to repress transcription at low micromolar concentrations [31]. Remarkably, however, native Alba had no repressive effect at these concentrations. The difference appears to be due to the presence of an acetyl lysine moiety at position Lys16 of native Alba. The effect of acetylation is to lower the affinity of Alba for DNA by at least a factor of 30. Intriguingly, a sub-population of Alba in *Sulfolobus* extracts is found in complex with the *Sulfolobus* homologue of the eukaryotic histone deacetylase, Sir2. Furthermore, treatment of native Alba chromatin *in vitro* with Sir2 resulted in repression of transcription, presumably as a result of deacetylation of the Lys16 residue [31]. Thus, in a clear parallel with Eukaryotes, Archaea possess the capacity to modulate transcription through covalent modification of a key chromatin protein. Whether Sir2 is the only deacetylase that can modulate Alba is unknown. However, as can be seen in Table 1, although all Archaea that encode Sir2 homologues also have Alba, the converse is not always the case; that is, several Alba-containing Archaea do not encode a Sir2 homologue. Although it has not been demonstrated that Alba is acetylated in these species, it is possible that other deacetylases might exist. In this light, it is intriguing to note that many Archaea encode weak homologues of another eukaryotic histone deacetylase, the Rpd3 component of the transcriptional co-repressor complex, Sin3 [47]. The identity of the enzyme that acetylates Alba remains unknown, although sequence analysis of archaeal genomes indicates that many Archaea encode a homologue of the Elp3 acetyl transferase, first characterized in budding yeast [48,49]. However, some species that possess Elp3 homologues, for example *Methanosarcina mazei*, do not encode Alba. Thus, if Elp3 does acetylate Alba, it is clearly not the only substrate for this enzyme.

Future prospects

It appears that Archaea possess the rudiments of eukaryotic nuclear DNA-compaction systems. Many of the Euryarchaeota contain simplified versions of histones that are clearly capable of mediating a primary level of compaction. In *Sulfolobus*, which

lacks histones, this role could be carried out by the Sul7d family of proteins. Other Crenarchaea such as *Aeropyrum pernix* and *Pyrobaculum aerophilum* could also have species-specific solutions to this problem, in which case a screen for abundant DNA-binding proteins in these organisms might prove worthwhile. In Eukaryotes, the nucleosome is the basic unit of compaction; interaction with linker histones and other proteins leads to ever increasing levels of higher-order compaction. It is possible that Alba might have a role in orchestrating higher-order folding of DNA–histone or DNA–Sul7d nucleoprotein assemblies. The recent discovery of modulation of Alba activity by acetylation and deacetylation could be the tip of the iceberg in unveiling the machinery that exists within Archaea to modulate DNA accessibility to transcription and replication machineries. Clearly, exciting discoveries remain to be made that will shed light on both the evolution and mechanistic detail at the heart of both archaeal and eukaryotic chromatin regulation.

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