Histone-DNA assemblies in archaea : shaping the genome on the edge of life

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CHAPTER 7

General discussion

Archaea appeal to the imagination of many. As inhabitants of hydrothermal vents, salt lakes, deserts, polar ice, geysers and mines, they raise questions about the limits of terrestrial life. The prefix 'hyper' is connected to archaea, as some are described to live in hypersaline lakes and hyperarid polar deserts, or are hyperthermophilic (355-357). Although extremities draw attention, it should be noted that many archaea have been identified in more common habitats, such as soil, oceans and intestines of animals, places that are also occupied by bacteria and eukaryotes. It seems that many extremophilic and mesophilic archaea are connected via another 'hyper' term: the hypernucleosome. This mechanism of DNA compaction via a rod-shaped histone core around which DNA is wrapped, has thus far only been found in archaea. The existence of the hypernucleosome was hypothesized based on micrococcal nuclease (MNase) digestion experiments, and crystallography studies revealed that archaeal histones really can form these structures (165, 197). We showed that hypernucleosomes are formed in solution. Also, we have made predictions on the ability of histones to form hypernucleosomes, based on the sequences encoded by archaeal genomes.

Histone variants and high affinity sequences

Histones, of which variants are encoded in most archaea, form dimers, tetramers and larger multimers. The hypernucleosome is potentially a very versatile tool for genome compaction and transcription regulation. Histone variants can modulate the structure of the hypernucleosome, which may contribute to a dynamic system that regulates transcription. Expression of histone variants in response to environmental cues could alter the length, stability or position of the hypernucleosome, which in turn changes compaction or availability of promoters. Also, specific high affinity sequences in DNA may position hypernucleosomes or tetramer complexes. Like many unicellular organisms, histones are generally depleted from the promoter region (246). However, on an individual basis, promoters may be prone to histone binding, if histones or histone variants have a higher affinity to certain sequences.

Eukaryotes use expression of histone variants and histone positioning by high affinity sequences for transcription regulation (191, 358, 359). Histone variants are (often essential) elements in eukaryotic gene expression, stress response, development, DNA damage repair and chromatin organization (360-365). Defects may result in disease. High affinity sites directly influence transcription initiation and histone remodeling (366). Although functionality of histone variants and the existence and relevance of high affinity sequences has yet to be established in archaea, it is not unlikely that these factors have a significant effect on vital cellular processes in archaea in a similar way as they do in eukaryotes. As the eukaryotic domain branches off from the domain of archaea, eukaryotes may have inherited this system from the first eukaryotic common ancestor (FECA). Now that research on archaeal histones and evolution of archaea are gaining momentum, the functionality of histone variants and high affinity sequences in archaea becomes an urgent question to be addressed.

Interplay with other NAPs

Archaea express a number of nucleoid-associated proteins (NAPs), of which histones, the main focus of this thesis, are arguably the best-studied examples. However, many other NAPs are encoded by the genomes of archaea. Alba, MC1 and Dps are the most widespread examples. In this thesis we focus mainly on interactions between histones, but we should not ignore the interplay that histones may have with other NAPs, both directly and indirectly. Alba-coding genes are found in the majority of archaeal genomes, and Alba is able to differentially regulate gene expression (117, 367). Like histones, Alba is hypothesized to block the binding sites of the general transcription factors (GTFs), which are key elements in transcription initiation (117). Therefore it is important to know what factors influence the competition between Alba, histones and transcription factors. Post-translational modification of Alba alters its binding affinity, which allows for regulation of transcription initiation (119, 368). Alba is able to induce and constrain twist strain (200). In this way it may indirectly influence the binding of histones. Although this effect has not been studied for Alba together with histones, it has for the combination of the local twist-inducing transcription factor-like architectural protein TrmBL2 and one of the histones from *Thermococcus kodakarensis*. At a moderate level of twist strain, TrmBL2 is the dominant protein in terms of DNA binding, whereas at low and high superhelical densities, histones become the main DNA occupant (304). This effect may be explained by the fact that histones can both left- and right-handedly wrap DNA, which relieves twist strain. In contrast, TrmBL2 laterally binds DNA, a form of binding that benefits from a neutral superhelical density. TrmBL2 has been found in a very limited number of organisms, but Alba, as well as other proteins capable of altering or stabilizing twist, may influence histone occupancy and positioning in a similar way as TrmBL2. Furthermore, Alba exhibits DNA-binding properties similar to those of linker histones found in eukaryotes, which provides potential structural synergy in binding.

Another notable NAP is the poorly studied MC1, which, like histone dimers, induces kinks in the DNA. MC1 was suggested to be the main NAP in the euryarchaeal class Halobacteria and in the genus *Methanosarcina*, part of the euryarchaeal class Methanomicrobia (223, 228, 230). Although MC1 has not exclusively been found in above-mentioned class and genus, it is striking that the histones of these taxa are either predicted to not form hypernucleosomes, or to form hypernucleosomes that are likely non-essential for genome compaction and DNA organization. The hypothesis that hypernucleosome formation is in some cases non-essential, has been based on the notion that in some phyla, histones predicted to form hypernucleosomes are not equally distributed among its species, leaving some species without multimerizing histones. This suggests that MC1 plays a role in the compaction of the chromosome when hypernucleosomes are not formed. The function of MC1 in Halobacteria and Methanosarcina may be similar to that of the HU-family protein HTa, which also induces kinks in the DNA. HTa, expressed by *Thermoplasma acidophilum*, is the main NAP in a species of which the genome does not encode histones. It was hypothesized that HTa fills the architectural role that histones play in other archaea (235). Immunoprecipitation studies found that HTa is mainly located at compacted DNA (369). HTa has a histone-like nucleotide preference and is able to cover both short and long stretches of DNA, the abundance of which is growth phase dependent (235). Although not a sequential homolog of HTa, MC1 may play a similar role as HTa. This functional conservation has been widespread through all domains, as archaea, bacteria and eukaryotes express NAPs that can bend, bridge and wrap DNA in order to alter genome architecture on a global and local level (13).

Discovery and characterization of archaeal histones

The recent emergence of metagenomic sequencing has made available an enormous amount of genomic information, and with it a large number of histone sequences. Thanks to this information, the archaeal tree of life is rapidly expanding, and as a result, the gap between archaea and eukaryotes is narrowing. This gives insight in how processes such as transcription regulation and genome compaction have evolved. The identification of the Asgard archaea has not only resulted in the discovery of some thus far eukaryote-exclusive features in archaea, but also revealed new types of archaeal histones that ask for urgent characterization. The fraction of archaeal histones that have been experimentally investigated remains small to date, but high throughput single molecule technologies and systematic sequence analysis may rapidly lead to a better understanding of how histones interact with DNA, each other, histone variants and other NAPs, and it may shed light on what structures they form. The discovery of the hypernucleosome is an important lead in terms of characterization of histones. Questions about its length, its response to environmental cues and its role in transcription regulation remain to be answered. Chromosome conformation capture techniques, which have recently revealed the architecture of the chromosome of many eukaryotes and some bacteria, will soon gain a foothold in the archaeal field. It likely is able to give new insights in how the archaeal genome is organized, and may demonstrate what the role of histones is in archaeal genome organization.

The hypernucleosome formed by archaeal histones may not only give us a better understanding of how archaea organize their genomes, but it may also make more clear what the importance of genome organization is in all domains of life. As NAPs are functionally conserved, we may find similar mechanisms and structures in other parts of life. Thus far, hypernucleosomes have not been found in eukaryotes, but as all eukaryotes express histones, they may not be exclusive to archaea. This especially applies to the organisms that are most closely related to archaea. Also, the hypernucleosome likely is an important link that explains how NAPs have evolved over time. Until now, archaea have not been proven to cause human disease, but as more information on the archaeome of humans and animals becomes rapidly available, they may be identified as the cause of health problems in the near future. An accurate understanding of archaeal transcription regulation and genome architecture may make it a target for treatment. Also, archaea have been an important source for biocatalysts, and applications for 'extremozymes' range from flavor enhancing in the food and feed industry to ink production and the synthesis of pharmaceuticals (370). Not only extracted enzymes, but also whole cells are being used for biocatalysis (371). A better understanding of the archaeal transcription machinery may help in the design of future whole cell biocatalysts (372). Furthermore, the role of archaea on the global carbon, nitrogen and sulfur cycles is only emerging, while greenhouse gases, nitrate pollution and emission of sulfur oxides are more topical than ever. Insight into the archaeal DNA organization machinery could potentially also lead to a better comprehension of the contribution of archaea to geochemical cycles, which affect all life on earth.