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

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SUMMARY

All life on earth contains DNA, which is used to store biological information. Organisms compact their DNA in order for it to fit inside their cell(s). Specialized proteins, which are referred to as nucleoid-associated proteins (NAPs), help organize the DNA to keep it compact but accessible for transcription. These NAPs often function as DNA benders, bridgers and wrappers. In most eukaryotic and archaeal species, histones are important NAPs that are able to bend or wrap the DNA duplex around its core. In this thesis, the histones from archaea are described in terms of their interaction with DNA.

Archaea, sometimes referred to as the third domain of life besides eukaryotes and bacteria, are a group of single-cellular organisms that are found in nearly every habitat on earth. Although optically somewhat resembling bacteria, genetically they are more related to eukaryotes. Archaea have only been recognized as a separate domain since the 1970s. Their role in the global geochemical cycles is significant, and some components of archaea have found their way to technological applications. Although archaea are a prominent inhabitant of the human gut, their role in health and disease has largely to be established. In **CHAPTER 1**, we give a broad introduction of archaea as a domain. Also, this chapter gives an over-

view of transcription regulation in archaea on a molecular level. Furthermore, we introduce the eukaryotic and archaeal histone, and we highlight their main differences and similarities.

Recently, it was discovered that some archaeal histones assemble onto DNA as continuous, rod-like structures, which we named hypernucleosomes. In **CHAPTER 2**, we describe on a molecular level which components of the archaeal histone contribute to the formation of the hypernucleosome. We also analyze the primary structure of all archaeal histones known to date, and we predict if these histones together with DNA can potentially assemble into hypernucleosomes.

For the characterization of NAPs and their interaction with DNA, single molecule techniques can be a powerful tool. To study the effect of NAPs on DNA conformation, tethered particle motion (TPM) can be a very useful high-throughput method. In TPM, the root mean square displacement of a bead tethered to a glass slide via a DNA duplex gives a read-out of DNA conformation. NAP concentration and physico-chemical conditions can be varied in order to study their effect on NAP-DNA assemblies. In **CHAPTER 3**, we show how TPM can be used when studying NAPs. Also, we provide new ways of TPM data representation, which allow insight into how individual measurements contribute to the population average.

In **CHAPTER 4**, TPM is used to study how histones HMfA and HMfB from the archaeal organism *Methanothermus fervidus* compact DNA. In addition, we use magnetic tweezers to perform force spectroscopy experiments, from which we conclude that the hypernucleosome formed by HMfB is more robust than the one formed by HMfA. We furthermore investigate if the components that were predicted to contribute to hypernucleosome formation as described in chapter 2, indeed play a role in that process *in vitro*. Also, we perform twisting experiments, which show that HMfB hypernucleosomes are left-handed, but torque can drive their conformation to change to a right-handed structure.

Like *M. fervidus*, the genomes of some archaeal species encode multiple histones. An interesting example are the histones from the salt-loving species *Nanosalina* sp. J07AB43, belonging to the recently discovered phylum *Candidatus* Nanohaloarchaeota. In chapter 2, we predict that some of these histones may be able to form a hypernucleosome, whereas one particular Nanosalina histone is very unlikely to do so. In **CHAPTER 5**, we perform microscale thermophoresis (MST) experiments of which the results suggest that histone HA together with DNA assembles into hypernucleosomes, whereas HB does not. We also measure at very high salt concentrations, which better resembles the conditions in which species from *Ca.* Nanohaloarchaeota are found.

Since archaeal histones can compact parts of the genome, they are likely a part of the transcription regulation system. It is hypothesized that specific DNA sequences play a role in the positioning of archaeal histones onto the genome. In **CHAPTER 6**, the effect of a known specific sequence called Clone20 on *M. fervidus* histones is investigated. We find that these histones modestly compact Clone20 DNA at histone concentrations below 22 nM, whereas this does not happen on a random DNA sequence. Also, we propose mechanisms by which sequences like Clone20 may interplay with other elements of the archaeal transcription regulation system.

A broad discussion of the work presented in this thesis is given in **CHAPTER 7**.