Karolinska Institutet

Institutionen för Biovetenskaper och Näringslära

CHROMATIN REMODELERS AND THEIR ROLES IN CHROMATIN ORGANIZATION

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ABSTRACT

The DNA in the eukaryotic nucleus is organized into a complex DNA-protein structure called chromatin. The basic repeating unit of chromatin is the nucleosome, which consists of 147 bp of DNA wrapped around a histone protein octamer. The nucleosomes form a "beads on a string" structure, which can be folded into higher-order structures that allow an extensive degree of DNA compaction. This compaction is so effective that 2 meters of DNA can fit into the human cell nucleus with a diameter of only 10 μm. Hence, nucleosomes condense and organize the genome, but at the same time they occlude many regulatory elements essential for transcription, replication, repair and recombination. To ensure dynamic access to packaged DNA, cells have evolved a set of proteins called chromatin remodeling complexes, which actively restructure chromatin. These enzymes use the energy from ATP hydrolysis to unwrap, slide, and eject nucleosomes.

This thesis describes the roles of two families of ATP-dependent chromatin remodeling factors in chromatin regulation and organization in the model organism *Schizosaccharomyces pombe* (fission yeast).

We show that the CHD remodeling factor, Hrp1, promotes incorporation of the H3 histone variant CENP-A^{Cnp1} at centromeres and at a set of gene promoters. We suggest that Hrp1 participates in a remodeling process that evicts H3 from promoters, both in euchromatin and centromeric chromatin, which then facilitates CENP-A^{Cnp1} incorporation.

Furthermore, we demonstrate that the Fun30 remodeling factor, Fft3, regulates the chromatin structure over insulator elements and tethers them to the inner nuclear membrane close to nuclear pores. This organizes the chromatin into different domains and ensures correct chromatin structure and gene expression at silent domains.

Additionally, we have generated the first genome-wide map of nucleosome positions in *S. pombe*. This map revealed important differences from the related yeast *Saccharomyces cerevisiae*. The two yeasts showed differences in nucleosome spacing, the roles of DNA sequence features and in the regular nucleosome arrays. This argues against the existence of an evolutionarily conserved genomic code for nucleosome positioning. Instead, species-specific nucleosome positioning factors (e.g. chromatin remodeling complexes) appear to override the biophysical properties of the DNA sequence.

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