Institutionen för Biovetenskaper och Näringslära

CHROMATIN REMODELERS
AND THEIR ROLES IN
CHROMATIN ORGANIZATION

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska
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av

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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<sup>Cnp1</sup> 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<sup>Cnp1</sup>
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.