Structural Insights into the CAF-1 histone-binding domain and its interaction with H3-H4

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Résumé

One of the most basic function of a cell is its own division. Before this step, a cell must duplicate its genome, and in order to maintain its identity, its epigenome must be totally replicated or re-established. This process occurs in all living organisms during the G1-S and G2 phases of the cell cycle before mitosis, leading to the production of two identical DNA daughter strands embedded in an identical chromatin structure. During this process, nucleosomes are removed from DNA approximately 300 base pairs ahead of the replication fork, so that the replication machinery can act on naked DNA, and they are recycled onto the daughter strands while newly synthesized histones are imported in the nucleus to offset the doubling of the genetic material.
The histone chaperone Chromatin Assembly Factor 1 (CAF-1) is a key factor of this process as it reassembles histones H3-H4 onto newly synthesized DNA. CAF-1 activity is conserved among species [1]. The chaperone is composed of three subunits: p150, p60 and p48 in human and Pcf1, Pcf2 and Pcf3 in fission yeast. Based on biochemical studies, the actual proposed mechanism for histone H3-H4 deposition by CAF-1 involves first its binding to a single H3-H4 dimer, inducing a conformational rearrangement that promotes its interaction with the polymerase sliding clamp PCNA (proliferating cell nuclear antigen) and DNA. Two CAF-1H3-H4 complexes assemble a H3-H4 tetramer on DNA to achieve the first step of nucleosome assembly [2] [3][4]. Still, the molecular determinants of this mechanism remain poorly described.

I will present how we characterized the principal H3-H4 binding site of CAF-1 and its interaction with histones, by liquid-state NMR and other biophysical tools, and how this enabled us to design mutants that affect their interaction with histones.

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