Structure of the human inner kinetochore bound to a centromeric CENP-A nucleosome

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Accurate chromosome segregation, controlled by kinetochore-mediated chromatid attachments to the mitotic spindle, ensures the faithful inheritance of genetic information. Kinetochores assemble onto specialized CENP-A nucleosomes (CENP-A-Nuc) of centromeric chromatin. In humans, this is mostly organized as thousands of copies of an ~171 bp α-satellite repeat. I will present the structure of the human inner kinetochore CCAN (Constitutive Centromere Associated Network) complex bound to CENP-A-Nuc reconstituted onto α-satellite DNA, derived through a hybrid cryo-EM and X-ray crystallography approach. CCAN forms edge-on contacts with CENP-A-Nuc, while a linker DNA segment of the α-satellite repeat emerges from the fully-wrapped end of the nucleosome to thread through the central CENP-LN channel which tightly grips the DNA. The CENP-TWSX histone-fold module, together with CENP-HIKHead, further augments DNA binding and partially wraps the linker DNA in a manner reminiscent of canonical nucleosomes. Our findings suggest that the topological entrapment of the α-satellite repeat linker DNA by CCAN may provide a robust mechanism by which the kinetochore withstands the pushing and pulling of centromeres associated with chromosome congression and segregation forces.