Centromeres, kinetochores, and their specification

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Centromeres are specialized loci that initiate kinetochore assembly, which mediates chromosome segregation during mitosis and meiosis. Centromere protein A (CENP-A), a histone H3 variant, specifically localizes to centromeres and is essential for kinetochore assembly in humans and many other species. As an epigenetic marker, CENP-A's presence at centromeres isn't dependent on any particular DNA sequence. In metazoans, new CENP-A is deposited early in G1 to compensate for its dilution during DNA replication. A key question is how CENP-A is loaded onto chromatin without direct DNA sequence information. This question addresses the epigenetic basis of CENP-A specification. In my presentation, I will discuss our efforts to combine biochemical reconstitutions of CENP-A loading with cell biological assays to study its deposition in G1 and inheritance during DNA replication. Previous work identified a hexameric complex of Mis18α and Mis18β as essential for loading new CENP-A onto centromeric chromatin in human cells. M18BP1, which binds directly to the Mis18 complex, is required for kinetochore recruitment and recognizes epigenetic determinants in centromeric chromatin. Together, the Mis18 complex and M18BP1 recruit the CENP-A chaperone HJURP and PLK1 kinase, both necessary for CENP-A loading. Our findings show that M18BP1 recognizes centromeres through complex interactions with multiple CCAN subunits, a 16-protein complex involved in CENP-A binding. However, the exact features of the centromere recognized by M18BP1 remain unclear, requiring further analysis.