

MECHANISMS TO MAINTAIN CENTROMERE STABILITY IN HUMAN CELLS

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Human centromeres are composed of highly organized arrays of repetitive alpha satellite DNA. Extensive sequence homology of the repeats within each centromere indicates that homologous recombination (HR) plays an active role in maintaining the repeat structure, but also implies that this process must be tightly regulated to avoid loss of centromeric DNA, which could result in kinetochore malfunctions and cause genome instability. We hypothesize that the mechanism(s) that suppresses mitotic recombination at centromeres may become compromised during ageing and tumorigenesis, leading to aneuploidy. To test this, we have utilized the CO-FISH technique to monitor centromere recombination in proliferating human cells. We observed an increase in sister chromatid exchanges and rearrangements at centromeres of a variety of cancer cells. To investigate the underlying molecular mechanisms that maintain centromere integrity, we down-regulated the centromere-specific histone H3 variant CENP-A and observed an increase in centromeric re-arrangements in both cancer and primary cells. Additionally, as the level of CENP-A is altered during cellular senescence, our preliminary data indicate that cellular senescence also leads to an increase in centromeres rearrangements. While CENP-A is an epigenetic determinant for kinetochore formation, which is critical for microtubule attachment and chromosome segregation, induction of aberrant attachments during mitosis did not enhance centromere rearrangements. Thus, we suggest that CENP-A provides a mechanism to suppress centromere recombination independently of its role in regulating microtubule attachments. We are currently dissecting the mechanism by which CENP-A represses centromere re-arrangements and the consequences of the alpha-satellite repeats recombination. The potential mechanisms by which the centromere integrity is compromised during ageing and tumorigenesis will also be discussed.