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Genome stability: Interplay between Double Strand Break (DSB), chromatin mobility and SMC complexes.

Chromosome organization has recently emerged as essential for maintaining genome integrity. In the budding yeast, chromosomes follow a Rabl configuration where centromeres are clustered close to the nuclear envelope near the Microtubule Organization Center. The attachment of microtubules to kinetochores, multiprotein complexes associated with centromeres, ensures the faithful segregation of chromosomes. Remarkably, DSB only near centromeres, leads to an increase in global chromatin mobility that favors repair by homologous recombination, pointing to specific features of pericentromeres.

We investigate pericentromeric specificity by analyzing chromosome maintenance proteins required for chromosomes spatial folding in response to DSBs, focusing on the Smc5/6 complex. This complex is enriched at pericentromeres and recruited to DSBs. Moreover, the Smc5/6 complex is able to interact with microtubules through lysines K624, K631 and K667 of the Smc5 protein. Here we question the role of the microtubule-Smc5 interaction in genome integrity, by analyzing chromatin organization and DSB repair in a mutant where the two lysines (K624 and K631), present in the characteristic hinge of Smc5, are mutated into glutamic acid (smc5-2KE).

The 2KE mutations lead to declustering of centromeres and increased global chromatin mobility, specifically at pericentromeres, all correlated with a decreased binding to microtubules in vitro. This suggests an effect of microtubules attachment to kinetochore on pericentromeric chromatin organization. Moreover, we examined a potential link between DSB repair and Smc5-microtubule interaction. The smc5-2KE mutant showed a strong decrease in Non-homologous end joining (NHEJ) and HR repair suggesting a role of microtubules stabilization through the Smc5/6 complex in DNA damage repair.

Overall, our results show that the Smc5/6 complex controls the binding of microtubules to kinetochores via two lysines in Smc5, thereby limiting global chromatin mobility. Furthermore, our findings suggest that in addition to global mobility, the Smc5-microtubule interaction is required to promote DSB repair.

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