

95. COHESINS: LINKING CANCER AND MEIOSIS

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Improper transmission of genetic information from a cell to its daughters results in aneuploidy, a hall marker of cancer. Genes involved in the maintenance of genome stability are thus of great interest, and are potential targets for future therapies. The recently discovered multi-protein complex, called 'cohesin' serves as a chromosomal glue which plays an important role in chromosome segregation and DNA repair, guarding the cell against malignant transformation (2). In mitotic cells, cohesin complex comprises at least four proteins: RAD21 (also known as SCC1), SCC3, SMC1 and SMC3. All these cohesin subunits except RAD21 are required for meiosis in yeast (1). The RAD21 subunit is replaced by its meiosis-specific paralogue, REC8. Abundant evidence suggests that cohesin defects may have detrimental consequences for genome stability, such as aneuploidy as seen in the cells of malignant tumors and chromosomal birth disorders (e.g. Down's syndrome). To investigate the role of cohesins in chromosome stability and segregation in mammals, our laboratory cloned human and mouse homologs of yeast *Rad21* and *Rec8* genes. We recently produced the first cohesin mutant mice by targeted deletion of the *Rec8* gene. Abrogation of *Rec8* gene function results in sterility in both males and females, confirming that the essential role of *Rec8* in meiosis is conserved in mammals. Analysis of chromosome spreads of spermatocytes revealed that *Rec8* mutant cells display aberrant meiotic chromosomal structures. These studies may provide insight into chromosome segregation defects contributing to human disorders such as infertility and pathogenesis of cancer.

(1) Nasmyth, K. (2001) Disseminating the genome: joining, resolving, and separating sister chromatids during mitosis and meiosis. *Annu. Rev. Genet.* **35**, 673–745. (2) Michaelis, C., Ciosk, R. & Nasmyth, K. (1997) Cohesins: chromosomal proteins that prevent premature separation of sister chromatids. *Cell* **91**, 35–45.