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A Targeted Genetic Screen to Identify Meiotic Cohesin Regulators

Urja Patel
Cleveland State University

Emilia Kalutskaya
Cleveland State University

Alexis Brown
Cleveland State University

Ali Ahsan
Cleveland State University

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College of Sciences and Health Professions

Student Researchers: Urja Patel, Emilia Kalutskaya, Alexis Brown, and Ali Ahsan

Faculty Advisor: Aaron F. Severson

Abstract

During oogenesis in animals deficient for REC-8, a cohesin subunit required for sister chromatids cohesin (SCC), Co recombination fails and sister chromatids segregate away from one another prematurely in meiosis I. Consequently, zygotes inherit two copies of each chromosome. Chromosome segregation in meiosis II fails and the progeny of rec-8 mutant mothers usually survive as viable polyploids. In contrast, homologs segregate randomly during meiosis I in oocytes produced by spo-11 mutants, which lack the transesterase required for crossover recombination. This results in aneuploidy, and nearly all the embryos die. We have shown that mutations disrupting SCC mediated by REC-8 cohesion, but not the related COH-3/4 cohesion complex, dramatically suppress the lethality of spo-11 mutants (88% vs 8% viable). Thus, a screen for spo-11 suppressors can identify kleisin-specific regulators critical for the formation of healthy gametes, including factors required for loading of REC-8 cohesion, for stepwise release of SCC mediated by REC-8 cohesion and for establishment of SCC by REC-8 cohesion, for example, mutations within subunits of REC-8 cohesion or in factors that couple premeiotic DNA replication to SCC establishment. A pilot screen of 4000 haploid genomes identified three suppressors. The first cloned was a null allele of htp-3, which encodes a component of the synaptonemal complex. This mutation revealed differential loading mechanisms of REC-8 and COH-3/4 and demonstrated the first evidence that HTP-3 regulates cohesin. We will continue this screen to identify additional regulators. Our analysis will provide insight into how cohesion and SCC are regulated during C.elegans meiosis. We expect our results will be relevant to plants and mammals, which also require multiple, functionally specialized meiotic kleisins.