Mir465, THE X CHROMOSOME, AND HYBRID STERILITY

Hybrid sterility is among the most striking manifestations of reproductive barriers, ultimately driving reproductive isolation and speciation. A disproportionate contribution of the X chromosome has long been recognized in this process. Mouse hybrids between subspecies of Mus musculus provide an exceptional system to dissect this phenomenon, where male infertility arises from the interaction between meiotic regulation, recombination dynamics, and X-linked incompatibilities. Jansa et al. (1) reveal that the previously identified male sterility Hstx2 locus on the X chromosome corresponds to a copy-number variable Mir465 microRNA cluster, and identify this variation as a central determinant of hybrid male sterility.

In non-hybrid strains, Mir465 copy number lies within a physiological range that preserves the transcriptional programs required for efficient meiotic double-strand break (DSB) formation, crossover repair, and proper progression through pachytene. In hybrids, however, the asymmetric Mir465 dosage inherited from the two parental subspecies, due to differences in copy number, disrupts this balance. Dosage-dependent misregulation of Mir465 targets and alters the expression of key meiotic genes, shifts the timing and efficiency of DSB repair, and ultimately reduces crossover numbers below the threshold needed to stabilize homolog pairing. These defects are particularly severe on the X chromosome, where Mir465 resides and where meiotic regulation is already constrained by the requirement for meiotic sex chromosome inactivation (MSCI).

As a consequence, hybrid males exhibit pronounced asynapsis, activation of pachytene checkpoints, and apoptotic loss of spermatocytes, leading to reduced sperm output or complete sterility. Hybrid male infertility thus emerges not from Mir465 per se, but from divergence in Mir465 copy number and expression that destabilizes the X-linked control of meiosis.

A final point is that, in this system, speciation is driven by variation at a single, rapidly evolving locus; in this case it is a tandem-repeat locus,

which has an inherent tendency to undergo duplication or deletion, making it especially prone to copy-number variation. This is remarkable, because it shows how the expansion of one genomic element can be sufficient to tip the balance toward reproductive isolation. The effect is also strongly male-biased, consistent with the heightened vulnerability of male meiosis to regulatory perturbations. Spermatogenesis involves a tightly constrained transcriptional program, extensive chromatin remodeling and the unique challenge of meiotic sex-chromosome inactivation, all of which make the male germ-line particularly sensitive to dosage- and timing-related disruptions.

1. https://www.ncbi.nlm.nih.gov/pubmed/41037637