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Abstract

Genetics and genomics of hybrid sterility

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Abstract

Male-limited hybrid sterility restricts gene flow between the related species, an important pre-requisite of speciation. The F1 hybrid males of PWD/Ph female (M*us m. musculus* subspecies) and C57BL/6J or B6 male (*Mus m. domesticus*) are azoospermic and sterile (PB6F1), while the hybrids from the reciprocal (B6PF1) cross are semi fertile. A disproportionately large effect of the X chromosome (Chr) on hybrid male sterility is a widespread phenomenon accompanying the origin of new species. In the present study, we mapped two phenotypically distinct hybrid sterility loci *Hstx1* and *Hstx2* to a common 4.7 Mb region on Chr. X. Analysis of meiotic prophase I of PB6F1 sterile males revealed meiotic block at mid-late pachynema and the TUNEL assay showed apoptosis of arrested spermatocytes. In sterile males over 95% of pachytene spermatocytes showed one or more unsynapsed autosomes visualized by anti SYCP1, HORMAD2 and SYCP3 antibodies. The phosphorylated form of H2AFX histone, normally restricted only to XY chromosome containing sex body decorated unsynapsed autosomes while abnormal sex body engulfed one or two univalents in 90% of the mid-late pachynemas. The unsynapsed pachynema chromosomes were additionally decorated by ATR and RAD51/DMC1 indicating the persistence of unrepaired DNA double-strand breaks (DSBs).The analysis of expression of X-linked genes in individual cells by RNA FISH and genome-wide expression profiling by Affymetrix GeneChips revealed the failure of MSCI in mid-pachynema of PB6F1 sterile hybrids. We have also demonstrated that the above mentioned phenotypes are strongly linked to 4.7 Mb $Hstx2^{PWD}$ locus on Chr X. Oocytes of F1 hybrid females showed the same kind of synaptic problems but with the incidence reduced to half. Most of the oocytes with pachytene asynapsis were eliminated before birth. In contrast to the hybrid males of the same genotype, the incidence of oocytes with asynapsis was not changed by the *Prdm9* or *Hstx2* genotype. We also found that F1 hybrid females carrying homozygous $Hstx2^{PWD}$ allele are fertile contradicting Muller's dominance theory that attempts to explain Haldane's rule. To analyze the possible cause of meiotic asynapsis we compared genome-wide meiotic recombination rate by counting MLH1 nodules in the parental strains, a set of partially overlapping B6.PWD-Chr X. # sub-consomics and their sterile and fertile hybrids. Strikingly, we found the recombination rate-controlling locus in the same 4.7Mb interval as the *Hstx1/2* hybrid sterility gene. Overall, we dissected the genetic and mechanistic basis of F_1 hybrid sterility and its possible interconnection with genetics of meiotic recombination.