Dissertation

A novel perspective on PRDM9-directed meiotic recombination: How interallelic interactions between meiotic regulator PRDM9 and X-chromosomal hybrid sterility locus HstX2 regulate hybrid fertility phenotypes

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Abstract

Meiotic recombination between homologs is initiated in accessible chromatin loops along the genomes of many mammalian species. To induce recombination, chromatin is first made locally accessible for the meiotic recombination machinery through interprotein collaborations between the central Zinc finger protein PRDM9 with HELLS and Zcwpw1 as well as the proteins of the COMPASS-Complex. Recombination itself is induced by a number of recombinases, including Rec8, DMC1 and SPO11, which introduce double-stranded breaks (DSBs) at a subset of PRDM9-directed positions, mediate homology search, guide the broken ends towards each and eventually accomplish the physical exchange of homologous parental alleles through DSB-repair. The results of such meiotic recombination events are either rare reciprocal cross-overs (CO) or, more frequently, non-reciprocal non-crossovers (NCO). While all these processes appear to be standardized at first sight, the diverse outcomes of meiotic recombination, observable as haploid gametes with unique genomes, but also as a wide spectrum of fertility phenotypes. Especially in F1 hybrid males from crosses between female PWD (*Laboratory strain of Mus musculus musculus)* and male B6 mice (*Laboratory strain of Mus musculus domesticus*), F1 hybrid sterility (HS) results from allelic incompatibilities between heterozygous intersubspecific PRDM9 variants. Cytologically, the HS phenotype is characterized by asymmetric recombination landscapes with perturbated homology search, DSB repair and early meiotic breakdown. However, HS does not occur universally as other hybrid offspring, including the reciprocal cross of HS, remains fertile. This model led to the discovery of the X-linked hybrid sterility locus HstX2, which structurally differs between PWD and B6 mice and leads to sterility when the $HstX2^{PWD}$ is active in the PWD X B6 genome.

This work investigates which mechanistic role variants of PRDM9 and HstX2 play in functional meiosis of intra-(B6 X DBA) and intersubspecific (B6 X CAST) hybrids at the initiation stages of meiotic recombination.

The presented analyses reveal that HstX2 impacts spermatogenic processes at an earlier timepoint in intrasubspecific hybrids than in intersubspecific hybrids. Furthermore, a very active hybrid recombination hotspot is characterized, in intersubspecific B6 X CAST hybrids, undermining the role of novel PRDM9-directed hotspots for hybrid fertility. ChIP-sequencing together with *insilico* predictions confirm that, while this hotspot is unknown to both parental genomes, it allows functional homologous meiotic recombination in intersubspecific hybrids.