LABORATORY OF

MOUSE MOLECULAR GENETICS

Meiosis, Prdm9, genetics of hybrid sterility, meiotic sex chromosome inactivation, chromosome substitution mouse strains

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The group focuses on genetic factors affecting the first meiotic prophase in mouse hybrids between related subspecies. The lab identified the first hybrid sterility gene, *Prdm9*, in a vertebrate species. *Prdm9* (*Meisetz*), encoding a meiotic histone H3 lysine-4 and lysine-36 tri-methyltransferase, revealed its dual role as a single factor determining positions of the meiotic recombination hotspots and as a major hybrid sterility gene possibly involved in speciation.[5] The second hybrid sterility gene showing Dobzhansky-Muller incompatibility with *Prdm9* was mapped to a 2.7 Mb *Hstx2* locus on chromosome X.[1] The same interval includes a major gene regulator of meiotic recombination rate (*Balcova et al., PLoS Genet. 2016*). The third prerequisite for complete meiotic arrest and male infertility of the laboratory model of hybrid sterility (mouse strains PWD of *Mus m. musculus* and B6 of *Mus m. domesticus* subspecies) is the *musculus/domesticus* heterozygosity of the genetic background. To understand the effect of genetic background in more detail, strains of hybrid mice were constructed where a pair of chromosomes of one subspecies was substituted by the corresponding pair from the other subspecies using chromosome substitution strains. This generated hybrids with stretches of DNA that came entirely from a single subspecies. Having such a stretch of 27 million or more DNA base pairs fully restored synapsis in a given pair of chromosomes during meiosis. Hybrid sterility was reversed when synapsis was restored in the four chromosomes that were most strongly affected by asynapsis.[2] Chromosome substitution strains prepared by the group (*Gregorova et al., Genome Res. 2008*) were also employed for identification of meiotic DNA DSBs repaired by noncrossovers (gene conversion). NGS sequencing of 10 mouse chromosome substitution strains revealed 94 noncrossovers with the mean length of a conversion tract of 32 base pairs. The finding of a significant deficit of noncrossovers descending from asymmetric DSBs has implications for the molecular mechanism of hybrid sterility in mice from crosses between closely related subspecies (*Gergelits et al., Genetics, in review 2020*).

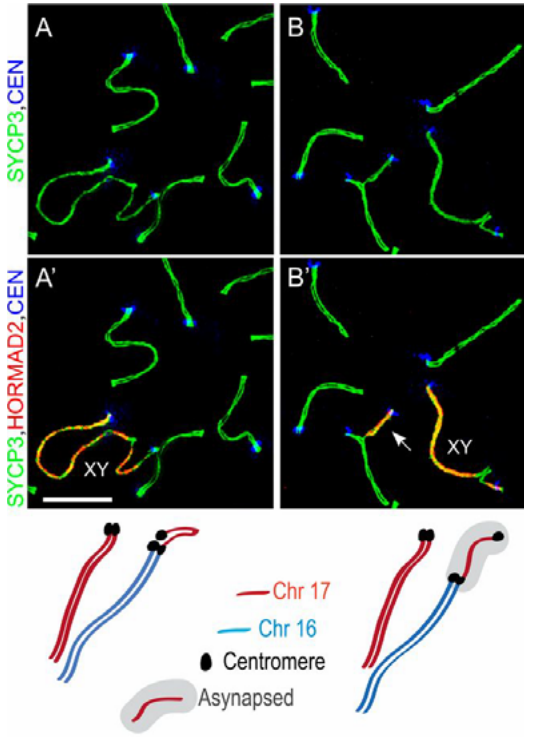

Figure 1. Super-resolution microscopy of synaptonemal complexes decorated by anti-SYCP3 antibody in pachytene spermatocytes of mice with T43Ts partial trisomy. The unsynapsed supernumerary copy of proximal chromosome 17 is folding to itself in the left cell or is left unpaired as a univalent decorated by HORMAD2 (arrow) on the right. Sex chromosomes are labelled XY. From Jansa et al., Biol Reprod. 124:1-9, 2014.

Selected publications:

1. Lustyk D, Kinsky S, Ullrich KK, Yancoskie M, Kasikova L, Gergelits V, Sedlacek R, Chan YF, Odenthal-Hesse L, Forejt J*, Jansa P* (2019) Genomic structure of *Hstx2* modifier of *Prdm9*-dependent hybrid male sterility in mice. *Genetics*, **213**:1047-1063.
2. Gregorova S, Gergelits V, Chvatalova I, Bhattacharyya T, Valiskova B, Fotopulosova V, Jansa P, Wiatrowska D, Forejt J* (2018) Modulation of *Prdm9*-controlled meiotic chromosome asynapsis overrides hybrid sterility in mice. *Elife*, **7**:pii: e34282. doi: 10.7554/eLife.34282, 2018.
3. Forejt J* (2016) Genetics: Asymmetric breaks in DNA cause sterility. *Nature*, **530**:167-8.
4. Bhattacharyya T, Gregorova S, Mihola O, Anger M., Sebestova J, Denny P, Simecek P, Forejt, J* (2013) Mechanistic basis of male infertility in mouse intersubspecific hybrids. *Proc Natl Acad Sci USA*, **110**:E468-77. doi: 10.1073/pnas.1219126110, 2013.
5. Mihola O, Trachtulec Z, Vlcek C, Schimenti JC, Forejt J* (2009) A mouse speciation gene encodes a meiotic Histone H3 methyltransferase. *Science*, **323**:373-375.

In the picture: 1. Gergelits Václav | 2. Parvanov Emil | 3. Forejt Jiří | 4. Jansa Petr | 5. Mukaj Amisa | 6. Fotopulosová Vladana | 7. Fusek Karel | 8. Lustyk (Wiatrowska) Diana