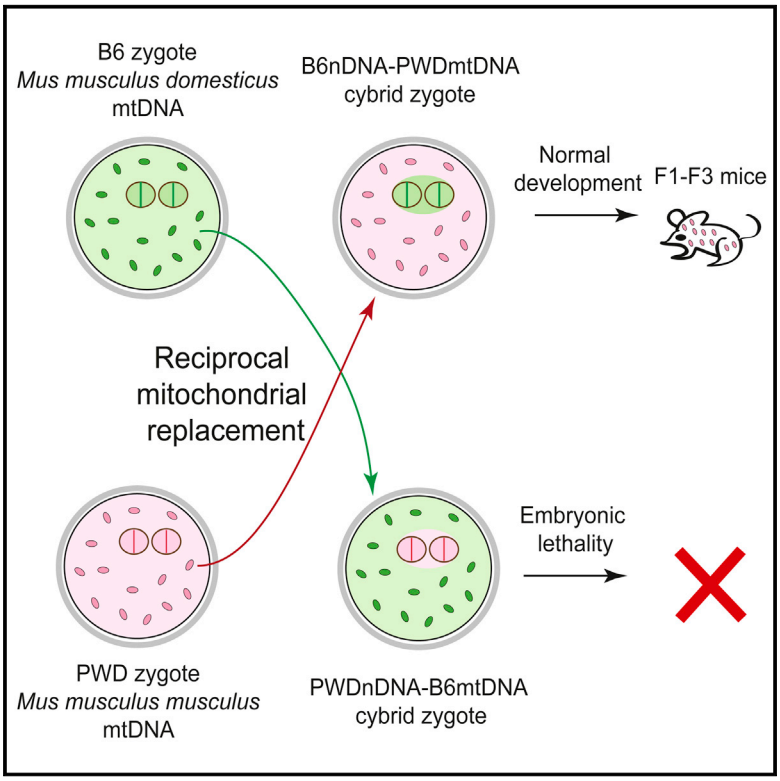
Article

Cell Metabolism

Incompatibility between Nuclear and Mitochondrial Genomes Contributes to an Interspecies Reproductive Barrier

Graphical Abstract



Highlights

- mtDNA replacement (MR) between B6 and PWD mice supports preimplantation development
- MR in PWD zygotes, but not in B6, caused post-implantation embryonic lethality
- Divergence of mtDNA contributes to interspecies reproductive isolation in mammals

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In Brief

Compatibility between nuclear and mitochondrial genomes is important for normal reproductive fitness. Mitalipov and colleagues show that reciprocal mtDNA replacement in zygotes between two mouse strains (B6 and PWD) results in post-implantation embryonic lethality, suggesting that mtDNA sequence divergence between mammalian species contributes to a reproductive barrier.

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Incompatibility between Nuclear and Mitochondrial Genomes Contributes to an Interspecies Reproductive Barrier

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SUMMARY

Vertebrate cells carry two different genomes, nuclear (nDNA) and mitochondrial (mtDNA), both encoding proteins involved in oxidative phosphorylation. Because of the extensive interactions, adaptive coevolution of the two genomes must occur to ensure normal mitochondrial function. To investigate whether incompatibilities between these two genomes could contribute to interspecies reproductive barriers, we performed reciprocal mtDNA replacement (MR) in zygotes between widely divergent *Mus m. domesticus* (B6) and conplastic *Mus m. musculus* (PWD) mice. Transfer of MR1 cybrid embryos (B6nDNA-PWDmtDNA) supported normal development of F1 offspring with reduced male fertility but unaffected reproductive fitness in females. Furthermore, donor PWD mtDNA was faithfully transmitted through the germline into F2 and F3 generations. In contrast, reciprocal MR2 (PWDnDNA-B6mtDNA) produced high embryonic loss and stillborn rates, suggesting an association between mitochondrial function and infertility. These results strongly suggest that functional incompatibility between nuclear and mitochondrial genomes contributes to interspecies reproductive isolation in mammals.

INTRODUCTION

Species divergence can occur when reproductive barriers between populations are established through breeding failure secondary to mating discrimination or failed fertilization because of gamete incompatibility (prezygotic isolation) (Lee et al., 2008; Rieseberg and Willis, 2007). Reproductive barriers can also involve detrimental hybrid postzygotic development because of chromosome number differences, chromosomal rearrangements, and other nDNA divergencies (Rieseberg and Willis, 2007). Moreover, nDNA to mtDNA incompatibility caused by sequence divergence may also play a major role in interspecies hybrid survival (Burton et al., 2013; Gershoni et al., 2009).

Maternally inherited mammalian mtDNA is typically present at high copy numbers (from hundreds to thousands) compared to only two copies of nuclear genes (Wallace, 2007). House mouse mtDNA is a 16,300 bp, double-stranded circular molecule encoding 13 mitochondrial proteins of OXPHOS, 2 ribosomal RNAs (rRNAs), and 22 transfer RNAs (tRNAs) (Koopman et al., 2012; McBride et al., 2006). The remaining OXPHOS proteins are encoded by the nuclear genome (Staubach et al., 2012). These protein subunits encoded by different genomes must be highly compatible to maintain the structural and biochemical properties required for uncompromised enzymatic function. Moreover, mtDNA replication, transcription, and translation are exclusively governed by factors encoded by nDNA (Woodson and Chory, 2008). Nuclear-encoded proteins must recognize and bind to regulatory motifs in mtDNA for proper function. Because of these close interactions, mitochondrial and nuclear genomes undergo adaptive co-evolution to maintain fitness in aerobic metabolism (Bayona-Bafaluy et al., 2005; Burton et al., 2013; Camus et al., 2015; Dowling et al., 2008; Pichaud et al., 2012; Wolff et al., 2014). Interspecies nDNA-mtDNA incompatibility is clearly demonstrated in experimentally induced, interspecies cytoplasmic hybrid (cybrid) cells when human mtDNA is maintained in the presence of great ape nuclear backgrounds, albeit with severe OXPHOS abnormalities (Bayona-Bafaluy et al., 2005). Moreover, mouse cybrid cells carrying rat mtDNA display a slower growth rate, reduced O_2 consumption, and reduced OXPHOS complex I and IV activities in the presence of normal mitochondrial protein synthesis. This combination could represent problems in the assembly of the OXPHOS system (Dey et al., 2000).

The impact of interspecies nDNA-mtDNA incompatibility on the organismal level is less obvious since reproductive barriers prevent the birth of live offspring in most hybrids. However,