Drosophila FMRP regulates microtubule network formation and axonal transport of mitochondria

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ABSTRACT

Fragile X syndrome, the most common form of inherited mental retardation, is caused by the absence of the fragile X mental retardation protein FMRP. The RNA-binding FMRP represses translation of the microtubule-associated protein 1B (MAP1B) during synaptogenesis in the brain of the neonatal mouse. However, the effect of FMRP on microtubules remains unclear. Mounting evidence shows that the structure and function of FMRP are well conserved across species from *Drosophila* to human. From a genetic screen, we identified *spastin* as a dominant suppressor of rough eye caused by *dfmr1* over-expression. *spastin* encodes a microtubule-severing protein and its mutations cause neurodegenerative hereditary spastic paraplegia. Epistatic and biochemical analysis revealed that *dfmr1* acts upstream of or in parallel with *spastin* in multiple processes, including synapse development, locomotive behaviour and microtubule network formation. Immunostaining showed that both loss- and gain-of-function mutations of *dfmr1* result in an apparently altered microtubule network. Western analysis revealed that the levels of α-tubulin and acetylated microtubules remained normal in *dfmr1* mutants but increased significantly when *dfmr1* was over-expressed. To examine the consequence of the aberrant microtubules in *dfmr1* mutants, we analysed the microtubule-dependent mitochondrial transport and found that the number of mitochondria and the flux of mitochondrial transport are negatively regulated by *dfmr1*. These results demonstrate that dFMRP plays a crucial role in controlling microtubule formation and mitochondrial transport. Thus, defective microtubules and abnormal mitochondrial transport might account for, at least partially, the pathogenesis of fragile X mental retardation.