Understanding translation dysfunction in fragile X-associated neural and reproductive disorders

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Germ cells alternate between periods of proliferation and developmental quiescence in many animals, and some germ cells, such as those found in primordial follicles in humans, can be maintained in an arrested state for up to five decades. We established *Drosophila* as a model system for understanding the genetic requirements of extended cellular quiescence by taking advantage of known physiologic checkpoints governing oocyte production, storage, and ovulation.

We subsequently identified *Fmr1* in a germline specific RNAi screen as a factor essential for the maintenance of arrested *Drosophila* oocytes. While arrested oocytes remain viable for several weeks following their production, oocytes lacking *Fmr1* become rapidly inviable, producing embryos with severe neuronal defects. We hypothesized that the loss of *Fmr1* in oocytes recapitulates molecular deficits that occur in the prominent human disorders fragile X-associated primary ovarian insufficiency and fragile X syndrome, which are linked to mutations in human *FMR1*.

Fmr1 is thought to regulate translation through repression of target transcripts; however, the identity of *Fmr1* targets and *Fmr1's* mode of action have remained elusive despite intensive study. Using ribosome profiling of arrested oocytes, we found that *Fmr1* functions as a translational activator rather than a repressor. *Fmr1* targets in oocytes include a large number of autism-related genes, whose unifying characteristic is their very large transcript size.

Translation of stored mRNAs in oocytes, neural synapses, and spermatocytes is linked to the presence of RNA-rich ribonucleoprotein (RNP) particles, which have been previously shown in cultured cells to be enriched for large transcripts which undergo translational repression. Our data suggest a requirement for *Fmr1* in preventing the translational repression of specific large stored transcripts, thereby maintaining the continuous production of key proteins that are essential for homeostasis.