

***Drosophila* FMRP participates in the DNA damage response by regulating G2/M cell cycle checkpoint and apoptosis**

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ABSTRACT

Fragile X syndrome (FXS), the most common form of inherited mental retardation, is caused by the loss of the fragile X mental retardation protein (FMRP). FMRP is a ubiquitously expressed, multi-domain RNA binding protein, but its *in vivo* function remains poorly understood. Recent studies have shown that FMRP participates in cell cycle control during development. Here we used *Drosophila* mutants to test if FMRP plays a role in DNA damage response under genotoxic stress. We found significantly fewer *dfmr1* mutants survived to adulthood than wild types following irradiation or exposure to chemical mutagens, demonstrating that loss of dFMRP results in hypersensitivity to genotoxic stress. Genotoxic stress significantly reduced mitotic cells in wild-type brains, indicating activation of a DNA damage-induced G2/M checkpoint, while mitosis was only moderately suppressed in *dfmr1* mutants. Elevated expression of cyclin B, a protein critical for the G2 to M transition, was observed in the larval brains of *dfmr1* mutants. *CycB* mRNA transcripts were enriched in the dFMRP-containing complex, suggesting that dFMRP regulates DNA damage induced G2/M checkpoint by repressing *CycB* mRNA translation. Reducing *CycB* dose by half in *dfmr1* mutants rescued the defective G2/M checkpoint and reversed hypersensitivity to genotoxic stress. In addition, *dfmr1* mutants exhibited more DNA breaks and elevated p53-dependent apoptosis following irradiation. Moreover, a loss-of-heterozygosity assay showed decreased irradiation-induced genome stability in *dfmr1* mutants. Thus, dFMRP maintains genome stability under genotoxic stress and regulates the G2/M DNA damage checkpoint by suppressing *CycB* expression.