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PROTEIN PHOSPHATASE 2A (PP2A) IS REQUIRED FOR THE MAINTENANCE OF *DROSOPHILA* CHROMOSOME INTEGRITY

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PP2A, chromosome aberrations, DNA repair foci, cell cycle

The processes through which cells sense and repair DNA lesions are collectively known as DNA damage response (DDR). Although Ser/Thr protein kinases have pivotal roles in the DDR, growing evidence indicates that these kinases and their substrates work in concert with numerous Ser/Thr phosphatases. One of the DDR key events is phosphorylation of the histone variant H2AX (H2Av in *Drosophila*) at the sites of DNA breakage to a form γ-*H2AX*, which recruits several additional DNA repair factors. These factors form discrete nuclear foci that dissolve when DNA repair is completed. Recent work has shown that completion of DNA repair requires dephosphorylation of γ-H2AX and that several phosphatases participate in this event. However, a direct evidence for a role of phosphatases in the maintenance of chromosome integrity is still lacking. We have isolated a lethal mutation, tws^{430}, in the *Drosophila twins (tws)* gene, that encodes the B regulative subunit of the Ser/Thr phosphatase 2A (PP2A). This mutation causes frequent (54%) chromosome aberrations (CAs) in larval neuroblasts. In addition, tws^{430} mutations affect the regression of IR-induced repair foci; in tws^{430} mutant brains the γ-H2Av foci persist much longer than in controls, suggesting that PP2A is required for γH2Av dephosphorylation. In tws^{430} mutants, the cell cycle does not slow down after IR-induced DNA damage. The mitotic index (MI) of wild type brains showed a strong decrease 15' after irradiation and remained lower than that of non-irradiated controls for two hours. In contrast, in irradiated tws^{430} mutant brains the MI was consistently similar to that of non-irradiated controls. These data indicate that PP2A may have a role also in the G2/M checkpoint. Double mutant analysis showed that mutations in *tefu* (ATM) are epistatic over mutations in *tws* (PP2A); in contrast *mei-41* (ATR) *tws* double mutants showed a significantly higher frequency of CAs than either single mutant. One appealing interpretation of these results is that *Drosophila* PP2A is primarily involved in dephosphorylation of ATM substrates, and that lack of *tws* activity results in the presence phosphorylated proteins that interfere with the normal DNA repair processes.