Protein phophatase 2A (PP2A) is required for the maintenance of *Drosophila* chromosome integrity

Chiara Merigliano[1], Antonio Marzio[2], Roberto Piergentili[2], Maurizio Gatti[1,2] and Fiammetta Vernì[1]

[1]Dipartimento di Biologia e Biotecnologie "C. Darwin", Sapienza, Università di Roma, and [2]Istituto di Biologia e Patologia Molecolari (IBPM) del CNR, P.le A. Moro 5, 00185 Roma, Italy.

(poster session)

ABSTRACT

The processes through which cells sense and repair DNA lesions are collectively known as DNA damage response (DDR). 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 g-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 g-H2AX and that several phosphatases participate in this event. We have isolated a lethal mutation, tws^{430}, in the *Drosophila twins* (*tws*) gene, which encodes the B regulative subunit of the Ser/Thr phosphatase 2A (PP2A). This mutation causes frequent (54%) chromosome aberrations (CABs) in larval neuroblasts. In addition, tws^{430} mutations affect the regression of IR-induced repair foci; in tws^{430} mutant brains the g-H2Av foci persist much longer than in controls, suggesting that PP2A is required for g-H2Av 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 CABs 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. We also found that RNAi-mediated downregulation of the B55 subunit of the human PP2A causes chromosome aberrations in HeLa cells. These results show the functional conservation of PP2A from *Drosophila* to humans, and suggest proper regulation of DNA repair foci is essential for the maintenance of chromosome integrity.