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BRCA2 Links DNA Damage to the Mitotic Checkpoint by Acetylating BubR1

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Germ-line mutations inactivating BRCA2 predispose to early-onset cancer as manifested by chromosome instability. Studies of BRCA2-deficient mouse suggest a crucial interplay between DNA repair and the mitotic checkpoint for the maintenance of genetic integrity. Here, we describe the molecular mechanism through which BRCA2 directly regulates the mitotic checkpoint. After severe DNA damage, BRCA2 and BubR1 formeda complex at the kinetochore in metaphase-arrested cells. Then, BRCA2, in complex with PCAF, acetylated BubR1 at K250 and inhibited ubiquitination-dependent proteolysis of BubR1. BubR1 was lost from the kinetochore in BRCA2-deficient cells and this was correlated with chromosome mis-segregation. Moreover, an acetylation-defective BubR1 mutant failed to activate the mitotic checkpoint. Collectively, these results suggest that BRCA2 coordinates DNA damage with the spindle checkpoint and that mutation of BRCA2 precipitates defects in DNA repair and mitotic checkpoint control, resulting in aneuploidy with aberrant chromosome translocations.

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