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“DNA Binding Region” of BRCA1 Affects Genetic Stability through modulating the Intra-S-Phase Checkpoint

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Abstarc :

The breast cancer associated gene 1 (BRCA1) contains 3 domains: an N-terminal RING domain with ubiquitin E3 ligase activity, C-terminal BRCT protein interaction domain and a central region. RING and BRCT domains are well characterized, yet the function of the central region remains unclear. In this study, we identified an essential DNA binding region (DBR: 421-701 amino acids) within the central region of human BRCA1, and found that BRCA1 brings DNA together and preferably binds to splayed-arm DNA in a sequence-independent manner. To investigate the biological role of the DBR, we generated mouse ES cells, which lack the DBR (?DBR) by using the TALEN method. The ?DBR cells exhibited decreased survival as compared to the wild type (WT) cells treated with a PARP inhibitor, however they have an intact ability to conduct DNA repair mediated by homologous recombination (HR). The ?DBR cells continued to incorporate more EdU in the presence of hydroxyurea (HU), which causes replication stress and exhibited reduced viability than the WT cells. Moreover, phosphorylation of CHK1, which regulates the intra-S phase checkpoint, was moderately decreased in ?DBR cells. These data suggest that DNA binding by BRCA1 affects the stability of DNA replication folks, resulting in weakened intra-S-phase checkpoint control in the ?DBR cells. The ?DBR cells also exhibited an increased number of abnormal chromosome structures as compared with WT cells, indicating that the ?DBR cells have increased genetic instability. Thus, we demonstrated that the DBR of BRCA1 modulates genetic stability through the intra-S-phase checkpoint activated by replication stress

Key Word :
BRCA1, DNA binding, Intra-S-phase checkpoint, Genomic instability

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