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学位論文の題名	CBP-93872 is an inhibitor of NBS1-mediated ATR activation that abrogates maintenance of the DNA-double-stranded break-specific G2 checkpoint （CBP-93872 は Nbs1 による ATR の活性化を阻害し、DNA 二重鎖切断による G2 チェックポイント維持を抑制する） Cancer Research 74, 3880-3889, 2014
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Maintaining the genomic stability of both normal cells and cancer cells depends on coordinated networks of different forms of the DNA damage response, which execute various cell activities such as cell-cycle arrest, apoptosis, and premature senescence. Abrogation of these systems likely leads to extensive genomic instability and subsequent cell death upon DNA damage. CBP-93872 was previously identified as a G_2 checkpoint inhibitor using a cell-based high-throughput screening system. However, its molecular actions as well as cellular targets are largely unknown. Here, we uncovered the molecular mechanisms underlying abrogation of the G_2 checkpoint by CBP-93872. CBP-93872 specifically abrogates the DNA double-stranded break (DSB)–induced G_2 checkpoint through inhibiting maintenance but not initiation of G_2 arrest because of specific inhibition of DSB-dependent ATR activation. Hence, ATR-dependent phosphorylation of Nbs1 and replication protein A 2 upon DSB was strongly suppressed in the presence of CBP-93872. CBP-93872 did not seem to inhibit DNA-end resection, but did inhibit Nbs1-dependent and ssDNA-induced ATR activation in vitro in a dose-dependent manner. Taken together, our results suggest that CBP-93872 is an inhibitor of maintenance of the DSB-specific G_2 checkpoint and thus might be a strong candidate as the basis for a drug that specifically sensitizes p53-mutated cancer cells to DSB-inducing DNA damage therapy.