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学位論文の題名	The ATR inhibitor AZD6738 increases the sensitivity of 5-fluorouracil in colorectal cancer cells by abrogating repair of DNA damage （ATR 阻害剤 AZD6738 は大腸癌細胞において DNA 損傷修復を無効化することで 5-FU の感受性を増加する） Oncology Reports, 47(4):78, 2022
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Abstract

Background:

The repair of DNA damage caused by chemotherapy in cancer cells occurs mainly at two cell cycle checkpoints (G1 and G2) and is a factor contributing to chemoresistance. Most colorectal cancers harbor mutations in p53, the main pathway involved in the G1 checkpoint, and thus are particularly dependent on the G2 checkpoint for DNA repair. We examined the effect of AZD6738, a specific inhibitor of the ATR kinase, involved in the G2 checkpoint, combined with 5-fluorouracil (5-FU), a central chemotherapeutic agent, on colorectal cancer cells.

Methods:

The effects of the AZD6738/5-FU combination were evaluated in various colorectal cancer cells by flow cytometry, western blotting, and WST-1 assay, as well as in an experimental animal model.

Results:

In vitro, the AZD6738/5-FU combination increased the number of mitotic cells according to flow cytometry, decreased the Chk1 phosphorylation level and increased cleaved caspase 3 and γH2AX levels according to western blotting, and decreased the proliferation rate of four colon cancer cell lines according to cell survival experiments. In vivo, xenografted colorectal cancer cells treated with the AZD6738/5-FU combination showed a significant decrease in proliferation.

Conclusion:

Our results suggest that AZD6738 enhances the effect of 5-FU in p53-mutated colorectal cancer.