学位の種類	博士（医学）
報告番号	甲第１９５１号
学位記番号	第１３８１号
氏名	原田 真之資
授与年月日	令和5年 3月 24日
学位論文の題名	AZD6738 promotes the tumor suppressive effects of trifluridine in colorectal cancer cells （AZD6738は大腸癌細胞におけるトリフルリジンの腫瘍抑制効果を促進する） Oncology Reports49: 52, 2023
論文審査担当者	主査： 片岡 洋望 副査： 稲垣 宏，髙橋 智

Abstract

【Introduction】

Ataxia telangiectasia and Rad3-related (ATR) is a kinase that repairs DNA damage. Although inhibitors that selectively target ATR have been developed, their effectiveness in colorectal cancer has not been widely reported. The present study hypothesized that anticancer agents that effectively act in the S phase before the G2/M checkpoint may be ideal agents for concomitant use with ATR inhibitors, which act at the G2/M checkpoint. The present study examined the combined effects of AZD6738, an ATR inhibitor, and trifluridine (FTD), which acts in the S phase and has a high DNA uptake rate.

【Methods】

In vitro cell viability assays, flow cytometry and western blotting were performed to evaluate cell viability, and changes in cell cycle localization and protein expression.
HT29, a BRAF-mutant cell line known to be resistant to anticancer drugs, was used to induce tumors in vivo.

【Results】

The results revealed that in colorectal cancer cells, the combination of AZD6738 and FTD inhibited cell viability, cell cycle arrest at the G2/M checkpoint and Chk1 phosphorylation, and increased apoptotic protein expression levels more than that when treated with FTD alone. FTD does not have sufficient efficacy when administered orally in vivo, it was mixed with tipiracil to prevent degradation; this mixture is known as TAS-102. TAS-102 alone exerted minimal tumor suppressive effects; however, when used in combination with AZD6738, tumor suppression was observed, suggesting that AZD6738 may increase the effectiveness of a weakly.

【Discusion】

Although ATR inhibitors are effective against p53 mutants, the present study demonstrated that these inhibitors were also effective against the p53 wild-type HCT116 colorectal cancer cell line.

In conclusion, combination therapy with AZD6738 and FTD enhanced the inhibition of tumor proliferation in vitro and in vivo. In the future, we aim to investigate the potentiating effect of AZD6738 on 5-fluouracil-resistant cell lines that are difficult to treat.