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Evaluating DNA damage and repair mechanism in TP53 wild-type and mutant medulloblastoma cell lines after AMG232 treatment combined with photon irradiation

Abstract
The tumour suppressor protein p53, encoded by the TP53 gene, plays a vital role in preventing tumour development. However, in numerous cancers, TP53 mutations or dysregulations result in compromised p53 functionality. AMG232, a potent MDM2 antagonist, has garnered attention for its potential to enhance tumour cell radiosensitivity. This study aimed to assess AMG232's efficacy in sensitizing medulloblastoma (MB) cells to photon irradiation via activation of the p53 pathway. Human MB cell lines, ONS-76 (TP53 wild-type) and DAOY (TP53 mutant), were exposed to photon irradiation and treated with AMG232, both as single and combined therapies. DNA damage was quantified through gamma-H2AX foci assays, revealing a significantly higher number of DNA damage foci in DAOY cells compared to ONS-76, indicating greater DNA damage and delayed repair kinetics. Notably, combined AMG232 and photon irradiation treatment resulted in a marked increase in DNA damage in ONS-76 cells relative to either treatment alone. In contrast, DAOY cells exhibited significant sensitivity to AMG232, independent of irradiation. The results suggest that AMG232 effectively enhances MB cell radiosensitivity, particularly in cells with functional TP53, while showing potential as a standalone treatment in cells with TP53 mutations. These findings indicate that AMG232 could be a valuable adjunct to radiotherapy in the management of high-grade brain tumours such as MB.
Keywords: p53 pathway, medulloblastoma, AMG232, DNA damage, photon irradiation

Notes

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