論 文 要 旨

Combination of hydroxyurea and tranilast suppresses gemcitabine resistance induced by ribonucleotide reductase M1 in gemcitabine-resistant cells

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ABSTRACT

Introduction: Gemcitabine (GEM; 2',2'-difluorodeoxycytidine) is widely used to treat pancreatic, biliary tract, non-small cell lung, bladder, mammary, and ovarian cancers. Chemoradiotherapy with GEM is a promising treatment for patients with advanced and locally recurrent head and neck cancers, including those with oral cavity cancer. However, the development of GEM resistance limits its use for curative treatment. Overexpression of ribonucleotide reductase (RR) M1 is a major cause of GEM resistance. We previously established RRM1-mediated GEM-resistant cell lines (MGEM6 and MGEM8) and showed that the knockdown of *RRM1* is a rationale strategy for overcoming GEM resistance. We further investigated the role of RR inhibition in enhancing the effects of GEM.

Materials and methods: We examined whether the combination treatment of hydroxyurea (HU), 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP), and tranilast (TRL) could increase GEM sensitivity using the survival assay of MGEM6, MGEM8, and their parental cells. The effects of these compounds on the expression of RRM1 and RRM2 mRNA and protein were evaluated in the three cell lines by quantitative PCR (polymerase chain reaction) and immunoblotting.

Results: HU or/and TRL at non-toxic concentrations significantly improved the response of resistant cancer cells to GEM, whereas 3-AP did not. This may have been because the two agents reduced the ratio of RRM1/RRM2. The three compounds have different effects on the mRNA and protein expression of RRM1 and RRM2.

Conclusions: The combination of HU and/or TRL with GEM enhances the toxic effect in gemcitabine-resistant cells induced by RRM1.