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Abstract

Photodynamic therapy (PDT) is an effective tumor treatment that involves the administration of a photosensitizer to generate cytotoxic $^1O_2$ [reactive oxygen species (ROS)] from molecular oxygen that is produced from energy absorption following tumor irradiation at specific wavelengths. Ferroptosis is induced by the disruption of the glutathione peroxidase 4 (GPX4) antioxidant system, leading to lipid peroxidation. We hypothesized that talaporfin sodium-photodynamic therapy (TS-PDT)-generated ROS would lead to ferroptosis via accumulation of lipid peroxidation. Cell viability assay in TS-PDT-treated cells in combination with a ferroptosis inhibitor (ferrostatin-1: Fer-1) or ferroptosis inducers (imidazole ketone erastin: IKE, Ras-selective lethal 3: RSL3) was performed. Accumulation of lipid peroxidation, GPX4 antioxidant system and cystine/glutamate antiporter (system xc^-) activity in TS-PDT-treated cells was investigated. In xenograft mice, the anti-tumor effect of TS-PDT in combination with ferroptosis inducers (IKE or sorafenib) was examined. TS-PDT-induced cell death was partly suppressed by Fer-1 and accompanied by lipid peroxidation. TS-PDT combined with IKE or RSL3 enhanced the induction of cell death. TS-PDT inhibited cystine uptake activity via system xc^-. *In vivo*, the combination of TS-PDT and ferroptosis inducers (IKE or sorafenib) reduced tumor volume. This study found that the mechanism underlying TS-PDT-induced ferroptosis constitutes direct lipid peroxidation by the generated ROS, and the inhibition of system xc^-, and that the combination of a ferroptosis inducer with TS-PDT enhances the antitumor effect of TS-PDT. Our findings suggest that ferroptosis-inducing therapies combined with PDT may benefit cancer patients significantly.