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Pseudolaric acid B triggers ferroptosis in glioma cells via activation of Nox4 and inhibition of xCT

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Abstract

Ferroptosis is a form of programmed cell death decided by iron-dependent lipid peroxidation, but its role in glioma cell death remains unclear. In this study, we found Pseudolaric acid B (PAB) inhibited the viabilities of glioma cells in vitro and in vivo, which was accompanied by abnormal increases of intracellular ferrous iron, H_2O_2 and lipid peroxidation, as well as depletion of GSH and cysteine. In vitro studies revealed that the lipid peroxidation and the cell death caused by PAB were both inhibited by iron chelator deferoxamine, but exacerbated by supplement of ferric ammonium citrate. Inhibition of lipid peroxidation with ferrostatin-1 or GSH rescued PAB-induced cell death. Morphologically, the cells treated with PAB presented intact membrane, shrunken mitochondria with increased membrane density, and normal-sized nucleus without chromatin condensation. Mechanistically, PAB improved intracellular iron by upregulation of transferrin receptor. The increased iron activated Nox4, which resulted in overproduction of H_2O_2 and lipid peroxides. Moreover, PAB depleted intracellular GSH via p53-mediated xCT pathway, which further exacerbated accumulation of H_2O_2 and lipid peroxides. Thus, PAB triggers ferroptosis in glioma cells and is a potential medicine for glioma treatment.