論 文 要 旨

Mitochondrial dysfunction promotes aquaporin expression that controls hydrogen peroxide permeability and ferroptosis

（ミトコンドリア機能障害は過酸化水素の膜透過性とフェロトーシスを制御するアクアポリンの発現を促進させる）

髙　裕子

Most anti-cancer agents and radiotherapy exert their therapeutic effects via the production of free radicals. Ferroptosis is a recently described cell death process that is accompanied by iron-dependent lipid peroxidation. Hydrogen peroxide (H_2O_2) has been reported to induce cell death. However, it remains controversial whether H_2O_2-induced cell death is ferroptosis. In the present study, we aimed to elucidate the involvement of mitochondria in H_2O_2-induced ferroptosis and examined the molecules that regulate ferroptosis. We found that one mechanism underlying H_2O_2-induced cell death is ferroptosis, which occurs soon after H_2O_2 treatment (within 3 h after H_2O_2treatment). We also investigated the involvement of mitochondria in H_2O_2-induced ferroptosis using mitochondrial DNA-depleted ρ^0 cells because ρ^0 cells produce more lipid peroxidation, hydroxyl radicals ($^{\bullet}OH$), and are more sensitive to H_2O_2 treatment. We found that ρ^0cells contain high Fe^{2+} levels that lead to $^{\bullet}OH$ production by H_2O_2. Further, we observed that aquaporin (AQP) 3, 5, and 8 bind nicotinamide-adenine dinucleotide phosphate oxidase 2 and regulate the permeability of extracellular H_2O_2, thereby contributing to ferroptosis. Additionally, the role of mitochondria in ferroptosis was investigated using mitochondrial transfer in ρ^0 cells. When mitochondria were transferred into ρ^0 cells, the cells exhibited no sensitivity to H_2O_2-induced cytotoxicity because of decreased Fe^{2+} levels. Moreover, mitochondrial transfer upregulated the mitochondrial quality control protein prohibitin 2 (PHB2), which contributes to reduced AQP expression. Our findings also revealed the involvement of AQP and PHB2 in ferroptosis. Our results indicate that H_2O_2 treatment enhances AQP expression, Fe^{2+} level, and lipid peroxidation, and decrease mitochondrial function by downregulating PHB2, and thus, is a promising modality for effective cancer treatment.