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CISD2 inhibition overcomes resistance to sulfasalazine-induced ferroptotic cell death in head and neck cancer

Eun Hye Kim, Daiha Shin, Jaewang Lee, Ah Ra Jung, Jong-Lyel Roh

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Abstract

Sulfasalazine has been repurposed to induce ferroptotic cancer cell death via inhibition of x_c^--cystine/glutamate antiporter (xCT). However, cancer cells are capable of developing mechanisms to evade cell death. Therefore, we sought to determine the molecular mechanisms underlying resistance to sulfasalazine-induced ferroptosis in head and neck cancer (HNC). The effects of sulfasalazine and pioglitazone were tested in various HNC cell lines. The effects of these drugs and inhibition and overexpression of CISD2 gene were determined by evaluating viability, cell death, lipid ROS production, mitochondrial iron, and mouse tumor xenograft models. SAS induced ferroptotic cell death in HNC at different levels. CISD2 expression showed an association between its expression and ferroptosis resistance. CISD2 overexpression conferred resistance to ferroptosis by sulfasalazine. Silencing CISD2 gene rendered resistant HNC cells susceptible to sulfasalazine-induced ferroptosis, with increased levels of lipid ROS and mitochondrial ferrous iron. Pioglitazone induced over-accumulation of mitochondrial iron and ROS and sensitized resistant HNC cells to sulfasalazine treatment *in vitro* and in a mouse tumor-xenograft model. CISD2 inhibition overcomes HNC resistance to ferroptotic cell death induced by sulfasalazine via increased accumulation of mitochondrial ferrous iron and lipid ROS.

Keywords: cancer resistance, ferroptosis, nutrient-deprivation autophagy factor-1, system x_c^- cystine/glutamate antiporter, pioglitazone