Exploring the Role of 7-Dehydrocholesterol and Lipid Alterations in Astrocytoma Resistance to Ferroptosis

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Introduction: Ferroptosis is a type of non-apoptotic cell death characterized by iron-dependent lipid peroxidation. 7-Dehydrocholesterol (7 DHC) has been demonstrated to shield cell membranes from phospholipid peroxidation linked to ferroptosis, owing to its high reactivity towards peroxyl radicals. Therefore, it is hypothesized that the accumulation of this cholesterol precursor may constitute an intrinsic mechanism in cancer cells to evade ferroptosis. Modulation of 7-DHC content can be achieved by inhibiting the activity of 7-dehydrocholesterol reductase (DHCR7), thereby concurrently reducing cholesterol levels. **Objective:** This study aimed to assess whether 7-dehydrocholesterol alters astrocytoma susceptibility to ferroptosis-induced cell death. **Materials and Methods:** Ferroptosis susceptibility was evaluated using a C6 astrocytic cell line (rat glioma) with pharmacological inhibition of the cholesterol synthesis pathway by AY9944. Ferroptosis was induced by treatment with the GPx4 inhibitor, RSL3. Lipid alterations induced by AY9944 treatment were assessed via global lipidomic analysis. **Results:** AY9944-treated cells exhibited increased resistance to cell death induced by ferroptosis. This protection was observed to stem not only from the accumulation of 7-DHC but also from overall lipid alterations, as identified through electrospray time-of-flight mass spectrometry (ESI-TOFMS) interfaced with ultrahigh performance liquid chromatography (UHPLC) analysis. Significantly elevated levels of cholesterol esters and triglycerides in treated cells suggest a potential accumulation of lipid droplets, which may play a crucial antioxidant role, thereby contributing to ferroptosis protection. **Conclusion:** This study advances our understanding of how cholesterol metabolism influences ferroptosis and aids in identifying potential targets for therapeutic development through manipulation of 7-DHC levels. Also, lipidomics of AY9944-treated astrocytoma cell line provided information about its lipid profile and remodeling, which may help to explain the observed increased resistance to ferroptosis.

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