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Heat shock factor-1 mitigates copper-induced DLAT protein aggregation

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Background: Cuproptosis, a non-apoptotic copper-induced cell death, is characterized by the aggregation of dihydrolipoamide S-acetyltransferase (DLAT), an essential enzyme involved in maintaining mitochondrial function and has been known to induce proteotoxic stress response (PSR). Heat shock factor 1 (HSF1), a master transcription regulator of PSR, is highly expressed in various cancer types and plays a chaperone role in protein folding and refolding to maintain protein stability. Cancer cells rely on this function to sustain their growth and proliferation. HSF1's ability to preserve proteomic stability is a key factor in its cytoprotective role, suggesting that HSF1 may contribute to the mechanisms that allow cancer cells to tolerate elevated copper accumulation. We aim to investigate the role of HSF1 in sustaining tumor viability in pancreatic ductal adenocarcinoma (PDAC) by mitigating copper-induced cytotoxicity.

Methods: In the human PDAC cell model, we used western blotting to analyze protein poly-ubiquitination, HSF1, and DLAT expression levels. Amyloid fibril formation was detected using a sandwich ELISA with an anti-OC antibody. Aggresomes were visualized using a fluorescence microscopy-based aggresome detection kit. The CellTiter-Blue® Cell Viability Assay was used to evaluate the cell viability. Non-reducing SDS-PAGE was performed to examine protein post-translational modifications.

Results: HSF1 overexpression effectively mitigates copper-induced protein ubiquitination and aggresome formation. Conversely, inhibiting HSF1 through knockdown or HSF1 inhibitor exacerbated the copper-increased amyloid fibril formation. Excess copper triggered DLAT aggregation and reduced its lipoylation, while HSF1 overexpression restored DLAT integrity and lipoylation levels. HSF1 inhibition enhanced the decrease in cell viability induced by copper-ionophore treatment in PDAC cells.

Conclusion: Our study highlights the protective role of HSF1 in mitigating copper-induced cellular toxicity in PDAC cells. Combining HSF1 inhibition with copper treatment presents a promising therapeutic strategy for targeting PDAC.

Keywords: HSF1, Copper, DLAT, Aggregation

