**Dihydrouridine synthase 2 sustains levels of tRNACys to inhibit ferroptosis in lung cancer**

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**ABSTRACT**

Dihydrouridine is a universal tRNA modification installed by conserved enzymes that are dysregulated in cancer. High dihydrouridine synthase 2 (DUS2) expression predicts poor patient outcomes in lung adenocarcinoma for reasons as yet unclear. Here, we investigated the mechanisms using human and mouse models and found that DUS2 suppresses ferroptosis, a metal-dependent non-apoptotic form of cell death that is emerging as a therapeutic target. DUS2 loss caused increased sensitivity to ferroptosis inducers with concomitant accumulation of toxic lipid peroxides, a hallmark of ferroptotic cell death. Mechanistically, DUS2 was specifically required to maintain tRNACysGCA levels to support translation of cysteine-rich proteins. We identified metallothioneins, which are 35% cysteine, as key regulators of ferroptosis downstream of DUS2 via their effects on metal and redox homeostasis. Combining DUS2 depletion with ferroptosis induction prolonged survival in a mouse model highlighting the therapeutic potential of targeting DUS2 in lung cancer.