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Targeting Ferroptosis Evasion Mechanisms in KRAS-Driven Lung Cancer

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Abstract

Ferroptosis is an oxidative, non-apoptotic form of cell death that is frequently inactivated in cancer, yet its regulation in oncogene-specific tumors remains poorly understood. We have identified lactate dehydrogenase B (LDHB), but not the closely related LDHA, as a noncanonical regulator of ferroptosis defense in KRAS-driven lung cancer. Using murine models and human-derived tumor cell lines, we demonstrate that LDHB silencing impairs glutathione (GSH) levels, sensitizing cancer cells to inhibitors of either GSH biosynthesis or utilization. This triggers a KRAS-specific ferroptosis-driven synthetic lethality, characterized by increased glutamine metabolism, oxidative phosphorylation (OXPHOS), and mitochondrial reactive oxygen species (mitoROS). Furthermore, we show that LDHB suppression upregulates STAT1, a negative regulator of SLC7A11, thereby reducing SLC7A11-dependent GSH metabolism. Our findings reveal a previously unrecognized role of LDH isoenzymes in ferroptosis resistance and provide a novel therapeutic rationale for targeting oncogene-specific ferroptosis susceptibility in KRAS-driven lung cancer.