ILF3 promotes colorectal cancer cell resistance to ferroptosis by enhancing cysteine uptake and GSH synthesis via stabilizing SLC3A2 mRNA

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Background: Ferroptosis is a type of programmed cell death characterized by iron accumulation and lipid peroxidation, has attracted considerable attention due to its close association with tumor metabolism, drug resistance, and the tumor immune microenvironment. In these past few years, RNA-binding proteins (RBPs) have emerged as key regulators of cancer biology through their roles in RNA processing, stability, and translation. Some previous also show that some RNA binding protein play essential roles in multiple biological processes in cancer, such as proliferation, apoptosis and autophagy. But currently, there are relatively few studies exploring the relationship between RNA binding protein and ferroptosis mechanism. Therefore the author want to use colorectal cancer (CRC) as a model to explore the relationship between RBPs and Ferroptosis.

Objective: This study aims to investigate the relationship between RNA binding protein and ferroptosis in colorectal cancer, and to provide a novel therapeutic target.

Results: Through RNA-seq profiling of CRC cells the researchers discovered that after treated with ferroptosis inducers RSL3, ILF3 was identified as the most significantly downregulated RBP. Further using western to confirm that only ILF3 protein was significantly down regulated. According to these findings they focus on investigating the mechanism of how ILF3 regulates ferroptosis. Functional validation using knockdown ILF3 CRC cells to demonstrate that ILF3 negatively regulates ferroptosis, as assessed by measured MDA level, and cell viability assays, and also further confirm by used mouse model. Mechanistically, RNA immunoprecipitation (RIP) and luciferase reporter assays confirmed that ILF3 directly binds to the 3′UTR of SLC3A2 mRNA, stabilizing its expression. This regulation maintained the activity of the system Xc- transport system, thereby increased cystine uptake, glutathione (GSH) biosynthesis, and NADPH generation and inhibit ferroptosis in the end therefore the CRC cells can proliferation. Clinically, immunohistochemistry of CRC specimens and Kaplan–Meier survival analysis revealed that high ILF3 and high SLC3A2expression correlates with poor overall survival. In RNA-seq data also revealed that TNF signaling pathway is one of ILF3-related pathway. So the author aim to investigate how TNF signaling pathway regulates ILF3. Collectively the data of co-immunoprecipitation(co-IP),ubiquitination assays and pull down assay showed that TRIM17 interacts with ILF3 and mediates its degradation through K29-linked polyubiquitination, a process that is disrupted when TNF-α is upregulated.

Conclusion: In summary, ILF3 maintains redox homeostasis and suppresses ferroptosis in CRC through post-transcriptional stabilization of SLC3A2 mRNA. The TRIM17/TNF-α axis further modulates ILF3 protein stability, highlighting a novel adaptive survival mechanism in CRC. These findings suggest that the ILF3–SLC3A2 pathway is not only a crucial regulator of ferroptosis but also a potential therapeutic target for overcoming resistance and improving CRC treatment outcomes.