**ALOX5 deficiency contributes to bladder cancer progression by mediating ferroptosis escape**

Liu T et al., Cell Death Dis. 2023 Dec 7;14(12):800.

 **Presenter:** Liu-Chia Jung **Date/Time:** 2024/04/25, 16:10-17:00

 **Commentator:** Dr. Wu-Li Wha **Location:** Room 601, Med College Building

**Background:** Bladder cancer (BCa) is one of the common malignant tumors of the urinary system. Currently, cisplatin-based chemotherapy remains the first-line treatment for muscle-invasive BCa (MIBC). However, only 40% patients benefit from it due to chemotherapy resistance and serious side-effects. Therefore, in-depth exploration and understanding of the molecular mechanism of BCa carcinogenesis and progression are essential to develop new therapeutic strategies to prolong the survival of advanced cancer patients. Ferroptosis is an iron-dependent form of regulated cell death driven by the accumulation of lethal lipid peroxides. Previous studies have demonstrated that inducing ferroptosis holds great potential in cancer therapy, especially for patients with traditional therapy failure. However, cancer cells can acquire ferroptosis evasion during progression. To date, the therapeutic potential of inducing ferroptosis in BCa remains unclear.

**Objective/Hypothesis:** To uncover a novel mechanism for BCa ferroptosis escape and propose that ALOX5 may be a valuable therapeutic target and prognostic biomarker in BCa treatment.

**Result:** First, they found that ferroptosis induction suppressed proliferation, migration, and invasion of BCa cells in vitro. Second, they found that high pathological stage BCa cells exhibited notably resistance to ferroptosis and abnormal lipid metabolism might be implicated in ferroptosis escape in BCa. Third, they conducted an RNAi-mediated loss-of-function screen experiment and a pharmacological inhibition assay to determine if the level of ALOX5 affected the sensitivity of BCa cells to ferroptosis in vitro. They used CRISPR/Cas9 technology to show that ALOX5 knockout increased ferroptosis resistance of BCa cells in vivo. They then validated the presence of EGR1 binding sites in the ALOX5 promoter by using both bioinformatics and chromatin immunoprecipitation (ChIP) assay. The qRT-PCR and WB assays confirmed that EGR1 indeed transcriptionally activated ALOX5 expression. In addition, they found that EGR1 could sensitize BCa cells to ferroptosis by transcriptionally activating ALOX5. Finally, they showed that the expression pattern of ALOX5 in BCa clinical specimens was negatively associated with tumor progression and outcome. Taken together, these clinical data confirm a strong association between ALOX5 and EGR1, highlighting the potential of ALOX5 as a promising prognostic indicator for BCa progression.

**Conclusion:** This study highlights the potential of ferroptosis induction as a promising therapeutic approach for low-stage BCa, while identifying its limitations in treating advanced tumors. Most importantly, their work uncovers a novel mechanism for BCa ferroptosis escape and proposes that ALOX5 may be a valuable therapeutic target and prognostic biomarker in BCa treatment.