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uL3 status influences ferroptotic cell death in p53-deleted colorectal cancer cells

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Abstract:
Targeting alternative cell death pathways is an innovative therapeutic approach to overcome chemoresistance in apoptosis-resistant cancer cells. We have previously demonstrated that ribosomal protein uL3 exerts a crucial role in drug-induced apoptotic pathway and its loss positively correlates with chemoresistance in colorectal cancer (CRC).
Here, we used the chicken chorioallantoic membrane (CAM) model to show that uL3 suppression promoted the metastatic capability of p53-deleted CRC cells. The differential expression analysis of RNA-Seq data evidenced ferroptosis-related genes as one of the most deregulated gene sets in CRC patients. Among them, we found an inverse correlation between SLC7A11 expression levels and uL3 levels. Of interest, inhibition of SLC7A11 with ferroptotic agent Erastin impaired resistant uL3-silenced CRC cell survival demonstrating that the susceptibility to ferroptosis may be used to treat resistant CRC cells. Notably, the combined treatment Erastin plus uL3 enhanced chemotherapeutic sensitivity of uL3-silenced CRC cells to Erastin also reducing their metastatic capability in CAM model. Taken together, these findings shed light on uL3-mediated chemoresistance and provides evidence of a novel therapeutic approach based on Erastin plus uL3 to induce ferroptosis. This strategy could provide the opportunity for personalized therapy by examining p53, uL3 and SLC7A11 profiles in tumors.

Keywords: colorectal cancer; drug resistance; SLC7A11/xCT; ferroptosis; ribosomal protein uL3; CAM assay