

Identification of regulators of ferroptotic cell death in melanoma

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Abstract

Given that lack of clinically available approaches to overcome resistance to modern targeted and immunotherapies for metastatic melanoma, a better understanding of cell death regulatory pathways are warranted in melanoma. Ferroptosis is a recently discovered lipid reactive oxygen radical-mediated, iron-dependent cell death that has shown particular promise in dedifferentiated, multi-drug resistant melanoma cell lines. However, it is unknown, why dedifferentiated melanoma cells are susceptible for ferroptotic cell death and why differentiated melanoma cells are resistant to ferroptosis.

Microphthalmia-associated transcription factor (MITF) is a critical regulator of melanocyte and melanoma differentiation and survival. Our preliminary results show that MITF transcription factor protects differentiated melanoma cells from cell death caused by ROS. **Bioinformatic analyses suggests that MITF mRNA levels inversely correlate with sensitivity to ferroptosis.** However, our preliminary *in vitro* functional experiments suggest that MITF functionally does not consistently affect sensitivity to ferroptosis. Thus, the **regulation of ferroptosis in melanoma remains largely uncharacterized.**

Our future aims are to identify new therapeutic targets promoting ferroptosis in differentiated and dedifferentiated melanoma cell lines by **performing genome-wide *in vitro* crispr screen assays to identify melanoma specific regulators of ferroptosis.** The expected outcome is the identification of several novel genes as therapeutic targets in preventing ferroptosis resistance in dedifferentiated melanoma and sensitizing differentiated melanoma cells to ferroptosis cell death.

