

## Reprogramming the reactivity of iron in cancer

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Mesenchymal cancer cells represent a small fraction of solid tumors at a given time point. Typically, these cells are refractory to conventional therapeutic agents. Furthermore, this cell state has been linked to the development of metastasis and cancer relapse. The complex natural product salinomycin has been shown to selectively kill this population of cells across lineages. It was previously proposed that salinomycin mediates its activity by increasing cellular concentrations of alkali metals such as sodium and potassium. To further illuminate mechanisms underlying the selective activity of salinomycin, we used a combination of synthetic organic chemistry, high-resolution microscopy and molecular biology techniques. In particular, we have shown that salinomycin and its synthetic derivatives accumulate in lysosomes and sequester iron in this organelle. As a result, accumulation of iron leads to the production of reactive oxygen species and lysosomal membrane permeabilization, which in turn promotes cell death by means of ferroptosis. These findings revealed the prevalence of iron homeostasis in mesenchymal cancer cells, paving the way towards the development of next generation therapeutics. Importantly, this work has led to the discovery that iron operates as a master regulator of cellular plasticity in the context of cancer.