Metal-optosis Warfare Against Cancer

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Cancer cells have a greater demand for iron and up-regulate iron uptake and down-regulate iron efflux by decreasing ferroportin (FPN) levels, thereby increasing iron retention. FPN levels have been negatively correlated with patient prognosis. This metabolic shift to a higher iron content also makes them potentially more vulnerable than non-cancer cells. We found that ferumoxytol (Feraheme; FH), an FDA-approved iron oxide nanoparticle, can be used as an anti-cancer therapy in leukemic cells where low FPN is a key signature. ROS produced by iron lead to increased oxidative stress and cell death through ferroptosis. Treatment with FH results in a significant reduction of disease burden in a murine acute myeloid leukemia (AML) model and patient-derived xenotransplants bearing leukemia cells with low ferroportin expression. We employed chelator free labeled ^{89}Zr-FH to image liver and spleen size in mice as well as track ^{89}Zr-FH distribution outside of these key organs. Mice administered ^{89}Zr-FH had an increased mean survival to controls and mice that died first had larger spleen sizes from disease burden. Importantly, we show an important path how to elicit ferroptosis with an already clinically approved agent and how to interrogate this biology with surrogate imaging makers. Further, we have now established an approach to not only treat leukemia with iron oxide nanoparticles but also now solid tumors and have gained a deeper understanding in the underlying biological drivers that determine therapy success or failure.

Recent studies have revealed that excessive Cu accumulation can trigger a novel form of cell death, known as cuproptosis, which is distinct from traditional cell death mechanisms like apoptosis. This unique process offers an innovative strategy for selectively targeting and eliminating cancer cells, as tumor cells tend to uptake more Cu ions than normal cells, providing greater specificity for both therapy and diagnosis. However, the clinical potential of Cu-based treatments is limited by the short half-life of Cu compounds in the body, which we are seeking to overcome by utilizing copper-based nanoparticles.

We show novel paths to utilize metal-based death mechanisms and to understand underlying biologies.