New Strategies Targeting Hypoxia and Iron Regulation in Kidney Cancer

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Genetic and functional studies within the past two decades have culminated in a paradigm that suggests a pro-tumorigenic role for HIF-2α, and a tumor suppressor role for HIF-1α in clear cell renal cell carcinoma (ccRCC), which has prompted the development of HIF-2α specific inhibitors. Through our efforts to identify selective small molecule inhibitors of HIF-2α, we have identified compounds that inhibit iron-responsive element (IRE)-mediated HIF-2α translation. These compounds act by disrupting cellular iron metabolism, which promotes the binding of iron-regulatory element binding protein 1 (IRP1) to the HIF-2α IRE, blocking HIF-2α translation. Intriguingly, treatment with these compounds also results in excessive iron accumulation and cell death via ferroptosis, a non-apoptotic form of cell death associated with iron-dependent lipid peroxidation. ccRCC cells are uniquely sensitive to ferroptosis due to the accumulation of poly-unsaturated lipids which gives them their distinctive clear cell morphology. Here, I will discuss the therapeutic potential of the dual targeting of HIF-2α and the induction of ferroptosis in ccRCC.