SIMULTANEOUS IRON CHELATION AND FERROPTOSIS INDUCTION AS A NOVEL ANTICANCER STRATEGY

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Iron is a vital micronutrient needed for the proper functioning of several enzymes involved in cellular metabolism, respiration and DNA replication. However, excess free iron leads to the generation of toxic reactive oxygen species and eventually triggers "ferroptosis", an iron-mediated programmed cell death**.** Deferasirox (DFX) is a cell-permeable iron chelator approved for the treatment of chronic iron overload. In this work, we report the synthesis and carachterization of its mitochondrially targeted derivative, called mitoDFX. Our agent exhibits markedly increase cytostatic, cytotoxic, and migrastatic properties when compared to DFX *in vitro*, while not affecting non-malignant cells. Mechanistically, mitoDFX significantly affects intramitochondrial iron levels and induces a loss of [Fe-S] cluster/heme containing enzymes. Furthermore, long-term incubation with mitoDFX dramatically affects the mitochondrial proteome. This results in dysfunctional mitochondria with markedly reduced respiration, disassembled respiratory supercomplexes and increased ROS production, all of which contribute to the induction of mitophagy. Importantly, mitoDFX leads to depletion of reduced glutathione levels and significant lipid peroxidation, pointing towards the activation of ferroptosis. In that line, *GPX4* KO or the addition of the glutathione synthesis inhibitor BSO synergize with the action of mitoDFX. Therefore, mitochondrial targeting of DFX represents a way to deprive cancer cells of biologically active iron, while exhausting their antioxidant defense mechanisms at the same time. Our findings highlight the novel concept of targeting mitochondrial iron metabolism as an anti-cancer approach and demonstrate that mitochondrially targeted deferasirox not only chelates the iron inside the mitochondria, but renders it redox-active, making mitoDFX an extremely effective anti-cancer drug.

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