TARGETING MITOCHONDRIAL IRON METABOLISM: A NEW APPROACH TO TREAT CANCER

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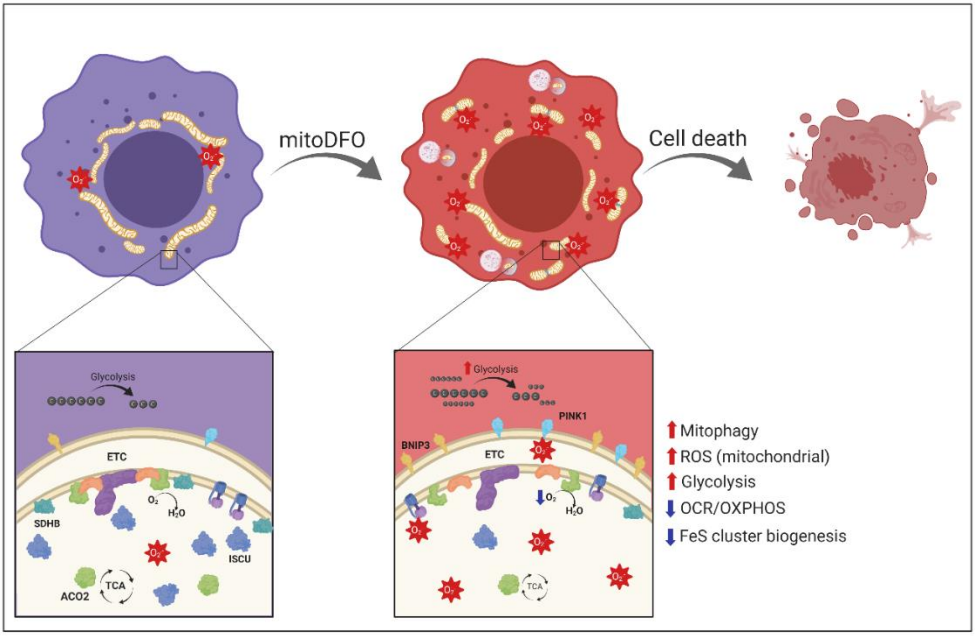
Abstract: Deferoxamine (DFO) represents a widely used iron chelator for the treatment of iron overload. Here we describe the use of mitochondrially targeted deferoxamine (mitoDFO) as a novel approach to preferentially target cancer cells. The agent showed marked cytostatic, cytotoxic, and migrastatic properties *in vitro*, and it significantly suppressed tumor growth and metastasis *in vivo*. The underlying molecular mechanisms included (I) impairment of [Fe-S] cluster/heme biogenesis, leading to destabilization and loss of activity of [Fe-S] cluster/heme containing enzymes, (II) inhibition of mitochondrial respiration leading to mitochondrial ROS production, resulting in dysfunctional mitochondria with markedly reduced supercomplexes, and (III) fragmentation of the mitochondrial network and induction of mitophagy[1]. Mitochondrial targeting of DFO represents a way to deprive cancer cells of biologically active iron, which is incompatible with their proliferation and invasion, without disrupting systemic iron metabolism. Our findings highlight the importance of mitochondrial iron metabolism for cancer cells and demonstrate repurposing deferoxamine into an effective anti-cancer drug *via* mitochondrial targeting.

Figure 1. Effects of mitoDFO on cancer cells



1. Sandoval-Acuña C, Torrealba N, Tomkova V, Jadhav S, Blazkova K, Merta L, Lettlova S, Adamcova MK, Rösel D, Brabek J, Neuzil J, Stursa J, Werner L, Truksa J. Targeting mitochondrial iron metabolism suppresses tumor growth and metastasis by inducing mitochondrial dysfunction and mitophagy. Cancer Research 2021, 81: 2289-2303.