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Engineered Anti-cancer therapy via mitochondrial targeted iron chelators

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Abstract

Iron is an essential micronutrient needed for the normal/ proper function of cellular enzymes involved in DNA replication and repair. It is also necessary for mitochondrial respiration and metabolism. For cancer cells it is a critical nutrient as these cells have generally higher iron requirements due to their active proliferation. Iron chelation in mitochondria, via our mitochondrially targeted compounds, leads to a selective cell death induction in cancer cells. This process involves respiratory supercomplexes disassembly, generation of reactive oxygen species (ROS), reduction in the activity of FeS cluster containing enzymes and induction of mitophagy. These compounds also significantly reduce tumor growth in vivo.

Here we present novel mitochondrially targeted compounds developed by our team. One of more than 10 synthetized iron-chelating derivatives is mitochondrially targeted deferoxamine (MitoDFO), an iron chelator well-known for the iron overload treatment. We now show that mitochondrial targeting of this drug substantially enhances its anti-cancer properties, inhibits migration and proliferation of cancer cells and also induces cell death. Our tests on non-malignant cells (epitomized by human fibroblast) also showed their significantly lower responsivity to the compound that indicates higher selectivity against cancer cells.

We have further tested the in vitro synergy between MitoDFO, which selectively modulates iron metabolism in cancer cells, and commonly used chemotherapeutic drugs that act via other routes including microtubule stabilization (paclitaxel) and DNA-synthesis inhibition (cis- platin, doxorubicin, 5-FU).

Complex synthesis and biological results of our compounds from in vitro and in vivo will be presented.

Biography

Kristyna Blazkova studied master degree at Department of Chemistry of Natural Compounds (UCT Prague) where she has been participating in projects specialised in carbohydrate chemistry. She has expertise in organic chemistry and for last 3 years has been mainly focusing on medicinal chemistry and especially on novel mitochondrially targeted substances with promising biological activity. She works as a scientist specialised in organic synthesis, in vitro and in vivo biological experiments in the Service technology laboratory (STL) at Institute of Biotechnology Czech Academy of Sciences.

Publications

1. Tuning the Nature of N-Based Groups From N-Containing Reduced Graphene Oxide: Enhanced Thermal Stability Using Post-Synthesis Treatments.
2. Identification of Protein Targets of Bioactive Small Molecules Using Randomly Photomodified Probes
3. Abstract B147: From bioactive small molecule to an identified protein target: A new method combining stochastic photomodification with a synthetic antibody mimetic
4. Polymers as tools for studying the internalization of membrane protein glutamate carboxypeptidase II
5. In Vivo Performance and Properties of Tamoxifen Metabolites for CreERT2 Control

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