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Synthesis and testing of mitochondria-targeted compounds

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Abstract

Although mitochondria have irreplaceable function in cells, their targeting for therapeutic applications is rather underexplored. As is becoming clear, the mitochondrion is not only a cellular powerhouse that synthetizes ATP, but also produces a number of biologically essential metabolites and is a relay point of a variety of signaling pathways. Many mitochondrial processes are highly conserved and/ or are important for organism survival. According to the free radical theory of aging, certain types of age-related disorders belong to mitochondrial diseases. Therefore, modulation of the mitochondrial functional status might help in some pathologies related to either mitochondrial function impairment or in the treatment of diseases which rely on highly functional mitochondria. Accordingly, this presentation will focus on a class of compounds that affect mitochondrial function. It will also describe methods of mitochondria targeting and the underlying mechanism of preferential accumulation of these agents into compartments with high trans membrane potential. Several possible areas of medicinal use of such compounds will be discussed. The story of the mitochondria-targeted tamoxifen (MitoTam), which is an inhibitor of mitochondrial respiratory complex I with ensuing anti-cancer activity will illustrate that mitochondrial targeting can lead to specific application of these compounds that we refer to as mitocans (standing for mitochondria and cancer). Specific targeting of complex I with MitoTam results in generation of high level of reactive oxygen species in mitochondria, resulting in efficient elimination of cancer cells. MitoTam is currently in Phase 1 clinical trial, and the background of its discovery, synthesis, manufacturing process optimization, preclinical development and mechanism of action will be discussed as well.

Furthermore, the antitumor effects of mitochondrially targeted derivatives of an iron chelator deferoxamine, which are able to disrupt iron metabolism, will be presented. These compounds pose significant migrastatic potential and are effective in suppression of experimental tumors in vivo.

Moreover, an approach to inhibit mitochondrial functional status in senescent cells will be shown. Due to a secretion of pro-inflammatory cytokines, especially TNFα, IL6, IL8 and IL1β are senescent cells associated with many age related pathologies. Hence, modulation of senescence associated secretory phenotype via implementing either senolytic or senomorphic compounds might be one of the cornerstones in the longevity research. Several other molecules (MitoQ, MitoVES, IACS-010759) which either enhance or diminish mitochondrial function will be presented/mentioned in context of current knowledge.

Biography

Lukas Werner has his background in medicinal and synthetic organic chemistry. He is the Head of the Service Technology Laboratory of the Institute of Biotechnology, Czech Academy of Sciences. The work of his team and co workers concerns both medicinal chemistry and medicinal development. He has over 10 patents relating to medicinal chemistry and new medicaments worldwide. One of the drugs he has been participating in development is currently in the Phase 1 clinical trial for oncological indications. His team is specialized in design and preclinical development of mitochondria targeted drugs with emphasis on hard-to-treat or orphan diseases.

Publications

1. Metformin directly targets the H3K27me3 demethylase KDM6A/UTX
2. Selective elimination of senescent cells by mitochondrial targeting is regulated by ANT2
3. Heteroatom analogues of hydrocodone: synthesis and biological activity
4. Heteroatom analogues of hydrocodone: synthesis and biological activity
5. Mitochondrial Targeting of Metformin Enhances Its Activity against Pancreatic Cancer
6. Selective Disruption of Respiratory Supercomplexes as a New Strategy to Suppress Her2 high Breast Cancer
7. Synthesis of buprenorphine from oripavine via N-demethylation of oripavine quaternary salts

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