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Mitochondria – a target for anticancer therapy

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Abstract

Mitochondria possess a central role in several cellular metabolic pathways, maintenance of calcium homeostasis, production of reactive oxygen species (ROS) and in the regulation of various cell death modalities. A majority of cancers demonstrate aberrations in mitochondrial functions, which were shown to contribute to tumourigenesis. In addition, many mechanisms of chemotherapy-resistance are located upstream of the mitochondria in cell death pathways. Thus, destabilization of mitochondria and permeabilization of the outer mitochondrial membrane (OMM), a point of no return in apoptosis induction, represent promising strategies for anticancer therapy. One major aim of this thesis was to identify therapeutic approaches to overcome resistance of cancer cells to conventional chemotherapeutic drugs. We could show in **Paper I** that chemotherapy resistance mechanisms in cancers, mediated by various oncogenic signalling/mutations, could be overcome by targeting Complex II of the mitochondrial respiratory chain. Treatment of Neuroblastoma (NB) cells with α-tocopheryl succinate (α-TOS), a redox-silent analogue of vitamin-E, which was shown to target Complex II, mediate ROS-production and an increase of cytosolic calcium levels, could induce apoptosis in cancers cells irrespective of their MycN or p53 status. We propose that this is based on the ability of α-TOS to induce both mechanisms of OMM permeabilization, in a Bax/Bak-dependent manner, as well as calcium-dependent induction of mitochondrial permeability transition (MPT).

In **Paper II and III** we investigated the possibility of sensitizing cancer cells to conventional anticancer drugs in a co-treatment setting with compounds targeting Complex II. In case of α-TOS **(Paper II)**, the obtained results revealed contrasting effects for the chemotherapeutic drugs etoposide and cisplatin. In case of etoposide, α-TOS was able to sensitize cancer cells in a dose-dependent manner. Whereas strikingly, in case of cisplatin, low concentration of α-TOS protected cells from cisplatin-induced toxicity. We demonstrated that the succinate moiety of α-TOS is mediating this protective effect via stimulation of Complex II activity. However, when Complex II was inhibited using thenoyltrifluoroacetone (TTFA) **(Paper III)**, a specific inhibitor of the ubiquinone binding site of Complex II, cells could be sensitized to both, etoposide- and cisplatin-induced cytotoxicity. This chemosensitizing effect was shown to rely on Complex II-mediated ROS-production.

For the study that was concluded in **Paper IV**, a different approach was utilized. Citrate, a substrate of the tricarboxylic acid cycle, was shown to induce cytotoxicity in cells. The underlying mechanism was speculated to be based on citrate's inhibitory effect on several crucial glycolytic enzymes and its ability to chelate calcium. We could demonstrate that although these features contribute, the main cause of cell death induced by citrate is the activation of initiator caspases. The underlying mechanism was proposed to be the kosmotropic property of citrate.

In summary, the findings of this PhD thesis clearly underline the potency of exploiting mitochondria for anticancer therapy. Particularly Complex II plays an intriguing role in the sensitivity towards chemotherapy and represents an attractive target that should be further explored in future projects. In addition, new roles of well-known mitochondrial substrates were revealed.