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Repurposing an anti-arrhythmic agent for cancer therapy

Desethylamiodarone (DEA) is a major metabolite of the widely used antiarrhythmic drug amiodarone. DEA accumulates in tissues up to a thousand times its therapeutic plasma concentration and has detrimental direct mitochondrial effects, as demonstrated previously using isolated mitochondria. Based on these properties, we proposed that the compound has potential use in cancer therapy and provided experimental evidence for its cytostatic and metastasis-limiting properties in human bladder, cervix, and melanoma cell lines *in vitro* and *in vivo*.

We demonstrated that DEA induced cell death, caused cell cycle arrest in the G0/G1 phase, and reduced colony formation at physiologically relevant concentrations *in vitro* in all said cell lines. Mechanistically, DEA shifted the Bax/Bcl-2 ratio to initiate apoptosis, promoted AIF nuclear translocation, activated PARP-1 cleavage and caspase-3 activation and reduced activation of the major cytoprotective kinases, ERK and Akt. All these effects are consistent with DEA's cytostatic properties. In a rodent experimental lung metastasis model, DEA attenuated *in vivo* metastasizing properties of B16-F10 human melanoma cells.

When revisiting DEA's mitochondrial effects in a metastasizing human melanoma line, it is found that it did not affect cellular oxygen radical formation. However, it did decrease the mitochondrial transmembrane potential, induced mitochondrial fragmentation, caused outer mitochondrial membrane permeabilization, and evoked a cyclosporine A–independent mitochondrial permeability transition. Energetically, DEA decreased maximal respiration, ATP production, coupling efficiency, glycolysis, and non-mitochondrial oxygen consumption. These mitochondrial effects likely contributed to the drug's cytostatic and anti-metastasizing properties.

We propose repurposing of DEA based on these data augmented by the fact that amiodarone is the most frequently prescribed antiarrhythmic drug and has been in therapy since 1961. Accordingly, safety concerns could be resolved more easily for DEA than for a novel pharmacological agent.

Recent Publications

1. Ferenc Gallyas, et.al (2022). Involvement of Mitochondrial Mechanisms and Cyclooxygenase-2 Activation in the Effect of Desethylamiodarone on 4T1 Triple-Negative Breast Cancer Line. International Journal of Molecular Sciences. 23. 1544.
2. Ferenc Gallyas, et.al (2021). Cyclophilin D-dependent mitochondrial permeability transition amplifies inflammatory reprogramming in endotoxemia. FEBS open bio 11 (3), 684-704
3. Ferenc Gallyas, et.al (2021). Mitochondrial protective effects of PARP-inhibition in hypertension-induced myocardial remodeling and in stressed cardiomyocytes. Life Sciences 268, 118936.

Biography

Ferec Gallyas has completed his M.sc in Chemistry in 1985. He worked for the Pharmacology Research Centre of Chemical Factory G. Richter Ltd. (Budapest, Hungary) as a researcher for 3 years before joining the University of Pecs Medical School (Pecs, Hungary), where he is a Full Professor and Head of the Department of Biochemistry and Medical Chemistry. He obtained his PhD in 1995 and DSc in 2008. He has co-authored more than 100 scientific publications, which have received more than 3500 citations, his publication H-index is 32, and he has been an invited speaker at several prestigious conferences. He is a member of seven Hungarian and three international scientific societies, Section Editor for PLoS One, editorial board member of Cancers and PeerJ, and is a reviewer for major journals and scientific foundations.

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