Editorial

Mitochondria as a Pharmacological Target: A Clue for Efficacy and a Reason for Toxicity

Mitochondria have been in the focus of intense biomedical research over the last 10 years. The complex participation of these organelles in cellular pathophysiology arises from their versatile function which includes bioenergetics, ROS generation and redox balance, Ca^{2+} homeostasis maintainance, thermogenesis, essential anabolic pathways as well as active regulation of several cell survival/death pathways. Importantly, mitochondrial dysfunction such as impaired oxidative phosphorylation and/or increased oxidative stress, together with the involvement of these organelles in apoptosis and the alterations of the selective process of their degradation, known as mitophagy, have been recently described as essential pathophysiological mechanisms, involved not only in "classical" human mitochondrial diseases but also actively engaged in the initiation, the development and the out-come of other congenital and acquired pathologies such as diabetes [1], cancer [2], cardiovascular diseases [3] and neurodegenerative disorders [4]. Pharmacological agents with mitochondrial action and selective mitochondria-targeted drugs display major therapeutic potential. In the field of liver cancer, Muntane J and coll. (IMIBIC, "Reina Sofia" University Hospital, Córdoba, Spain) describe that several mitocans such as Hexokinase II inhibitors, ETC and VDAC/ANT-targeting drugs as well as BH3 mimetics can induce apoptosis through mitochondrial depolarization and thus exerting an anti-tumor effect [2]. Also, the inhibition of the glucose transport or glycolysis (fasentin, apigenin, the polyphenolic compounds WZB27 and WZB115) has been suggested as a promising anti-cancer treatment. Victor VM and coll. (University Hospital Doctor Peset Foundation and University of Valencia, Valencia, Spain) review the beneficial effects of mitochondrial modulation in diabetes and diabetes-related disorders such as diabetic kidney disease [1]. Mainly *in vitro* studies have proven useful several antioxidants such as idebenone (CoQ10 analogue), overexpression of antioxidant enzymes and small SOD mimetic molecules, however their beneficial effects have not always been reproduced in animal models or humans. There is evidence however, that selective targeting of mitochondria with specific compounds such as MitoQ, a mitochondria-targeted antioxidant, promises to be an efficient therapeutic strategy for mitochondrial protection in diabetes. In addition, mitochondria-targeted therapy is also relevant as a pharmacological approach for aging and neurodegenerative diseases such as Parkinsons´s Disease, Alzheimer´s disease and amyotrophic lateral sclerosis [4]. Serviddio G and coll. (Department of Medical and Occupational Sciences, University of Foggia, Foggia, Italy) review the effects of lipophilic cations such as MitoQ, MitoVitE and MitoPBN, Szeto-Schiller (SS) peptides, TAT fusion peptides and protein conjugates with mitochondria signal peptides (MSP). Novel mitochondria-targeted molecules such as XJB-5-131 and the multifunctional envelope-type nano-device (MEND) have also been described [4]. Two reviews of this thematic issue focus on mitochondrial turnover processes such as mitochondrial biogenesis and particularly mitophagy as novel/future avenues for pharmacological intervention [3,5]. Among other cardioprotective mitochondrial agents and stimuli, Gottlieb RA and coll. (BioScience Center, San Diego State University, San Diego, CA, USA) specifically point to caloric restriction, exercise and the use of resveratrol, a natural stilbenoid with antioxidant properties, as triggers of mitophagy and biogenesis [3]. Goldman SJ and Taylor R (Veterinary Support & Oversight Branch, U.S. Army Research Institute of Environmental Medicine, Natick, MA, USA) provide a detailed review of the cellular mechanisms involved in autophagy/mitophagy and their relation with the pathogenesis of neurodegeneration and cardiovascular diseases. Many of these conditions manifest accumulation of abnormal mitochondria and alterations in mitochondrial dynamics [5]. Our increasing understanding of the mitophagy-related diseases generates an expanding list of potential targets for pharmacological interventions which call to be explored. Mitochondrial therapeutics can also be relevant to the management of chronic parasitic infections exemplified in Chagas disease, a common trypanosomiasis. In a comprehensive review, Silber AM and coll. (Departament of Parasitology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brasil) provide an insight into *Trypanosoma cruzi* mitochondria as drug targets [6]. The aminoacid metabolism has been given special emphasis. Several aminoacid-metabolizing enzymes such as arginine kinase and proline racemase as well some mitochondrial enzymes such as NADH-fumarate reductase have the potential to be specific targets in Chagas treatment as they have been indentified in the parasite but are absent in mammalian cells. *T. cruzi* also displays specificities regarding mitochondrial energetics and ROS generation which can be pharmacologically exploited. For instance, the fact that this parasite lacks catalase and peroxidase but possesses tryparedoxins, trypanothione and trypanothione reductase, homologues of which do not exist in the mammalian host, is an important issue in trypanoicidal drug engineering [6].

In summary, considering these very promising findings, it seems that modulation of mitochondrial function will be pursued in the novel therapeutic strategies designed to combat some of the current most common human diseases.

On the other side, there is a rapidly growing list of drug-induced mitochondrial effects which can lead to the generation of severe drug-related adverse events [7]. The interaction of drugs of clinical interest with specific mitochondrial targets and the repercussion of such interactions need to be evaluated in detail. This will certainly unable the prognosis and the treatment of a great number of drug-related detrimental reactions. Moreover, drug-induced mitotoxicity has been suggested to even contribute to the development of other mitochondria-related pathologies. Several drug groups (anti-diabetic, lipid-lowering drugs, antiretrovirals, NSAID) have been attributed mitochondrial toxicity and this occurs through different mechanisms including interference with bionergetics, ROS generation, mitochondria-mediated apoptosis, mtDNA replication etc. This has been described by Nadanaciva S and Will Y (Compound Safety Prediction, Pfizer Global R&D, Groton, CT, USA) who also provide a thorough overview of the methodological and technical challenges in detection of drug-induced mitotoxicity [7]. Doxorubicin (DXR) is one of the most potent anti-cancer agents employed in clinical practice. Despite the fact that clinicians have been aware of its cardiotoxic effects for nearly 20 years now, DXR is still used. Oliveira PJ and coll. (Center for Neuroscience and Cell Biology, Department of Life Sciences, University of Coimbra, Coimbra, Portugal) delve in the complex mitochondrial role present in the cardiotoxic effects induced by this drug and provide some insights in the way that DXR-associated toxicity could be prevented or monitored. Finally, they also provide clues about the intriguing question regarding the organ-specificity of the toxic effect induced by DXR and its relation with other organs and tissues [8]. An interesting approach to combat drug-induced cardiac mitotoxicity is offered by the use of drug-induced mitochondrial protection, as suggested for the non-selective β-blocker carvedilol. A beneficial outcome of such interaction has been shown in DXR-treated rats and some promising results have been obtained in human clinical trails [8]. A very complex mitochondrial implication has also been reported for the antiretroviral drugs applied in HIV treatment and this constitutes the origin of many clinically relevant adverse events related to this therapy, including myopathy, neuropathy, alterations in the lipid metabolism and hepatotoxicity. The review by Apostolova N and coll. (Faculty of Medicine, University of Valencia and CIBERehd, Valencia, Spain) scrutinizes the long list of mitochondrial mechanisms of interference associated with these drugs which includes besides the traditional target Pol-γ, the solely DNA polymerase responsible for mtDNA replication, several other, mtDNA-independent effects. One such interaction is the direct inhibitory action

on ETC and the process of oxidative phosphorylation. These reactions are particularly important for protease inhibitors and NNRTI- groups of anti-HIV drugs which do not impair mtDNA replication and whose mitochondrial effects are largely unexplored [9].

In all, the intense and rapidly developing mitochondrial research has produced a new field of biomedical knowledge denominated "mitochondrial pharmacology". Its present projection is to explore novel drug targets and drug-induced mechanisms of mitochondrial dysfunction in addition to dissecting the basic mitochondrial involvement in cellular pathogenic processes. All these findings have the final aim to generate models for successful mitochondrial therapeutic management.

ABBREVIATIONS

ETC	=	Electron transport chain
mtDNA	=	Mitochondrial DNA
NNRTI	=	Non-nucleoside reverse transcriptase inhibitors
NSAID	=	Non-steroidal anti-inflammatory drugs
ROS	=	Reactive oxygen species
VDAC/ANT	=	Voltage-dependent anion channel/Adenine nucleotide translocator

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