Advanced Drug Delivery Reviews 60 (2008) 1437–1438

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Preface

Mitochondrial medicine and mitochondrion-based therapeutics☆

Mitochondrial dysfunction is inherent in a variety of human disorders from the classical mitochondrial diseases arising from mitochondrial DNA mutations (encephalomyopathies) to those involving mitochondrial signaling pathways to the rest of the cell, modulated by organellar dynamics and culminating in programmed cell death. Beyond minding the cell's energy status, mitochondria are major cellular sources (and targets) of free radicals, play key roles in the regulation of calcium homeostasis, and are effectors of the intrinsic apoptotic pathway due to the release of signaling molecules that activate and trigger specific caspase cascades. The electron-transfer protein cytochrome *c* has been recognized over 20 years ago as a signaling molecule released from mitochondria, thus changing the view of these organelles from their energy-transducing functions to a regulatory role in cell death pathways. Hence, it is not surprising that treatment of mitochondrial dysfunction and development of mitochondrion-targeted therapeutics have become a primary focus of scientific research.

This issue of *Advanced Drug Delivery Reviews* covers a variety of perspectives on mitochondrion-targeted therapeutics and represents an authoritative and comprehensive treatise of several aspects of mitochondrial function in human disease ranging from the identification of potential drug targets of mitochondrial pathways to the development of specific drug delivery systems to mitochondria.

Hideyoshi Harashima and Yuma Yamada provide an overview of mitochondrion-targeted therapeutics and describe a number of mitochondrial protein and gene delivery systems and mitochondrion-based therapeutic strategies encompassing liposome-based delivery systems that use a multifunctional envelope-type nano device and membrane-fusion mechanisms. Of note, this variety of therapeutic approaches requires the understanding of the character of mitochondrial dysfunction affecting their role in energy-transducing processes, the generation of reactive oxygen species, and modulation of programmed cell death.

Under a section on Mitochondrial Energy Metabolism in Disease, Gerald Münch and his colleagues address the clinical benefits of lipoic acid as a neuroprotective agent in Alzheimer's disease; lipoic acid – a cofactor of the mitochondrial enzymes pyruvate dehydrogenase and α-ketoglutarate dehydrogenase – has been used rather successfully in the treatment of diabetic neuropathies and can interfere with the pathogenesis or progression of Alzheimer's disease. An important concept to this approach is that energy deficiencies arising from a decreased mitochondrial pyruvate dehydrogenase activity are early events in the pathogenesis of Alzheimer's disease that precede the appearance of the histopathological landmarks of this disorder. This chapter also contains a discussion on the pharmacokinetics of lipoic acid as well as combined treatments with an assortment of nutraceuticals. Based on the mechanistic features of the potassium channels in the inner mitochondrial membrane and the respiratory chain-based oxidative phosphorylation, David Busija and his colleagues establish the platform for mitochondrion-target preconditioning, in which the transient exposure to an initiating event is linked to protection of neurons against the subsequent lethal stimuli. Mitochondrial preconditioning – resulting in the maintenance of normal mitochondrial morphology, decrease formation of oxidants, and prevention of apoptosis – gains further significance because of its involvement in the regulation of intracellular signaling in a neuroprotective manner. The treatment of genetic mitochondrial diseases with dichloroacetate is addressed by Peter Stacpoole and his colleagues: this chapter again emphasizes the importance of pyruvate dehydrogenase in energy metabolism and the enzyme complex being a primary site of action of dichloroacetate. A sound rationale is offered for novel therapeutic approaches encompassing combined dichloroacetate and gene therapy treatments and their feasibility in the treatment of children with pyruvate dehydrogenase deficiency. Jamal Ibdah and his group identify the mitochondrial trifunctional protein – involved in β-oxidation of fatty acids – as a novel therapeutic target that goes beyond the usual dietary approaches of patients with recessively inherited mitochondrial trifunctional protein defects and partly entails the targeting of molecules involved in increasing hepatic fatty acid oxidation and using the appealing TAT–mitochondrial trifunctional protein (MPT) fusion proteins.

In a section on Mitochondria, oxidative stress, and degenerative diseases, the organelles are viewed as primary sources of reactive oxygen and nitrogen species and the mitochondrial pathways involved in this process are identified as potential therapeutic targets. Roderick Capaldi and his group at MitoSciences and the University of Oregon – based on the evidence for the accumulation of oxidative damage in the etiology of a variety of human diseases – focus on overcoming the pitfalls of technologies aimed at detection oxidative damage in mitochondria, cells, and tissues by offering solid methodologies to measure the fingerprints of oxidative and nitrative modifications of proteins: the development of an antibody-based immunocapture array for mitochondrial proteins involved in free radical generation and energy production is described. The therapeutic implications for the prevention of Alzheimer's disease in terms of estrogen regulation of aerobic and anaerobic glycolysis are discussed by Roberta D. Brinton: novel hypotheses, such as the 'healthy cell bias of estrogen action', link the estrogen-mediated activation of signaling pathway to mitochondrial regulation of aerobic glycolysis and identifies the time when neuronal health is not yet compromised for the initiation of estrogen therapy. The use of fluorescent probes coupled to digital imaging microscopy in order to detect oxidative

☆ This preface is part of the Advanced Drug Delivery Reviews theme issue on "Mitochondrial Medicine and Mitochondrion-Based Therapeutics".

0169-409X/$ – see front matter © 2008 Published by Elsevier B.V.
doi:10.1016/j.addr.2008.07.001

stress insult-induced mitochondrial oxidant production by astrocytes is discussed in detail by Mei-Jie Jou, who advances innovative concepts of relevance for protective 'preconditioning' and entailing a mitochondrial reactive oxygen species-mediated firewall. These views are also examined in the context of mitochondrion-targeted and nano-antioxidants and their overall effect on astrocyte function. Jean C. Shih writes about monoamine oxidases A and B, enzymes present in the mitochondrial outer membrane, their function, the neurotoxic potential of their reaction byproducts — among them reactive oxygen species, their level of expression and activity related to mitochondrial dysfunction and neurodegenerative disturbances, and their association with specific behavioral patterns. Monoamine oxidase inhibitors are well-established therapeutic approaches in a wide array of neuropsychiatric disorders.

The role of mitochondria in normal aging has been the focus of extensive research in the last 15 years and being complementary to and maturing from the free radical theory of aging, to the oxidative stress theory of aging, to the mitochondrial oxidative stress theory of aging, and today addressing the tight co-regulation of mitochondrial energy and redox signaling. In the section on Mitochondrial function and aging, Navarro and Boveris concentrate on a major regulatory mechanism of the mitochondrial energy — redox axis, the mitochondrial isoform of nitric oxide synthase, its changes with aging, and the role of mitochondrially generated nitric oxide in determining cell function and fate. It follows that strategies aimed at regulating mitochondrial nitric oxide activity as well as 'mitochondrion-targeted antioxidants' offer novel therapeutic avenues based on the premise that both mitochondrially generated species and signaling molecules – nitric oxide and hydrogen peroxide – report a high energy charge to the cytosol. The mitochondrial redox status is addressed by Rebrin and Sohal in terms of thiol/disulfide exchange – the glutathione redox status – during aging: perturbations in glutathione metabolism play a causal role in the aging process and, as a corollary, the understanding the mechanisms of age-related oxidizing shift in the glutathione redox status leads to the recognition of therapeutic strategies of relevance for normal aging.

The clinical implications for mitochondrial disease are addressed in two chapters: Stanley Murachevic discusses the clinical implications of uncommon syndromes due to errors in mitochondrial DNA as well as syndromes of disease states that apparently reflect a disrupted mitochondrial function and strengthens the significance of mitochondrial bioenergetics in caring for patients with mitochondrial disorders. Mark Tarnopolsky's mitochondrial cocktail offers a sound rationale for combined nutraceutical therapies in mitochondrial diseases that target the major notions described here: decreased energy-transducing activity, formation of reactive oxygen species, and signaling apoptotic or necrotic pathways. Hence, the action of mitochondrion-specific antioxidants combined with essential cofactors for energy-transducing activities and alternative energy sources represent a multifaceted approach to the therapy of mitochondrial cytopathies.

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