Editorial

VDAC As a Pharmaceutical Target

Mitochondria play a pivotal role in maintaining and regulating metabolic function of cells and organs, working in fundamental ways that concern permeability of mitochondrial membranes, energy supply and the synthesis of several compounds, including lipid precursors, iron-sulfur clusters and nucleotides. For these reasons, many human diseases such as cardiovascular disease, neurodegeneration, cancer and aging are strictly associated with noticeable and progressive mitochondrial dysfunction. In particular, oxidative damage, disruption of mitochondrial ATP synthesis, calcium dyshomeostasis or induction of the outer mitochondrial membrane permeabilization (OMMP) establishes a deregulation of mitochondrial metabolism even leading to mitochondrial distruction (mitophagy) or cell death.

The Voltage-Dependent Anion selective Channel (VDAC) is the main channel and the most abundant integral membrane protein of the outer mitochondrial membrane (OMM) where it forms hydrophilic pores. VDAC is considered the master regulator of mitochondrial metabolism due to its crucial action for metabolic and energetic substrates from and to the organelle. Thus, VDAC1 appears to be a convergence point for a variety of cell survival and death signals, mediated *via* association with ligands and proteins. It is also co-responsible for various cell processes including apoptosis, calcium homeostasis and many different diseases, such as cancer. Deficiency of VDAC has been associated with a lethal encephalomyopathy.

In this special issue, different aspects of VDAC involvement in the physiopathology of serious human diseases are presented, focusing on the action of possible molecules able to act as drugs. Considering the central role of cell death in diseases, VDAC-interacting proteins are undoubtedly important for VDAC-mediated cell death pathways. Overall, VDAC as a pharmacological target against cancer, neurodegenerative and cerebro- or cardiovascular diseases is a very promising field.

The first review, by Karachitos, Jordan and Kmita, addresses the effects of VDACs-interacting molecules on cytoprotection and mitochondrial physiology in cerebrovascular and cardiovascular diseases. The authors summarize the available data regarding the action on myocardial infarction or on cardiomyocyte apoptosis of many proteins directly interacting with VDAC, like CRYAB, neuroglobin or α–enolase. These proteines, as well as others, use VDAC1 as a docking site on the mitochondrial surface. They also discuss the possible contribution to cyto- and cardioprotection of drugs that directly interact with VDAC1, like fluoxetine, 4,4′-diisothiocyanostilbene-2,2′-disulfonic acid (DIDS) or minocycline. The effects of implications for ischemic stroke and myocardial ischemia of molecules indirectly interacting with VDAC, like GSK-3β, are also discussed. Moreover, the VDAC-targeted drugs with a putative cytoprotective effect are also considered. As the main therapeutic approach for cerebrovascular and cardiovascular diseases appears to require efficient cell protection against death, compounds exerting their cytoprotection effect by direct or indirect interaction with VDAC could be used for therapeutic aim.

The contribution by Shoshan-Barmatz, Krelin and Chen takes into consideration the VDAC1 function in apoptosis, focusing on VDAC1 oligomerization as a key step in mitochondria-mediated apoptosis. VDAC1 oligomerization plays important physiological roles in the regulation of VDAC1 function, stabilizing the protein and serving as a platform for other proteins that oligomerize, such as hexokinases (HKs) or creatine kinase, and also mediating Cyto *c* release and the binding of apoptosis-regulating proteins. In this review, the authors present several molecules leading to VDAC1 oligomerization, such as cyathin-R, cisplatin and selenite. They also discuss VDAC1-interacting molecules able to inhibit VDAC1 oligomerization and apoptosis, such as 4-acetamido-4′-isothiocyanato-stilbene-2,2′-disulfonic acid (SITS), diphenylamine-2-carboxylate (DPC), ruthenium red and VBIT-4. The effect of different apoptosis inducers inducing VDAC1 over-expression is also considered, as well as the important relationship between VDAC1 expression levels and drug sensitivity.

Along this line, in the paper by Reina and De Pinto, data from the literature are recapitulated, describing compounds acting on model cancerous proliferation through VDAC. VDAC represents indeed an interesting target for cancer treatment because of its central location in the bioenergetics metabolism and its involvement in several cellular processes. The authors arrange these VDAC-interacting drug molecules into three main categories, according to their mechanism of action: molecules acting on the VDAC-hexokinase binding, molecules directly inhibiting the

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lar processes. The authors arrange these VDAC-interacting drug molecules into three main categories, according to their mechanism of action: molecules acting on the VDAC-hexokinase binding, molecules directly inhibiting the VDAC conductance, molecules affecting the expression levels of the VDAC gene. Old and more recently discovered molecules are reported, like Oroxylin A, Methyl jasmonate, Avicins, or Cyathin-R. Moreover, peptides and miRNA acting on VDAC1 as therapeutic tools against cancer are also considered.

In my review, Andrea Magrì and I described the roles of VDAC isoforms, particularly of VDAC1, in the most commom neurological disorders. A prevalent feature of neurodegenerative diseases is the misfolding of specific key proteins and VDACs are known to act as a favorite docking site at the mitochondrial level also for some misfolded proteins. These non physiological interactions modify the VDAC1 conductance leading to a bioenergetic impairment with a dramatic effect on the cell viability. In detail, this review analyzes imolecules and peptides available so far, able to interact and modulate VDAC1 in Alzheimer's, Parkinson's or Huntington's disease, and also in Amyotrophic Lateral Sclerosis. An overview of the literature is presented focusing on the mechanisms implicated in the mitochondrial dysfunction due to the interaction of VDAC with Aβ peptides, Tau, α-synuclein (αSyn) or mutated SOD1. The effect of molecules able to inibit these interaction, such as the Hesperidin or the NHK1 peptide, is also treated. Overall, this review offers a description of the most promising known molecules acting on VDAC1 potentially useful in new therapeutic strategies for the treatment of neurodegenerative diseases.

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