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Minireview

New findings concerning vertebrate porin II — On the relevance of glycine motifs of type-1 VDAC

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ABSTRACT

New findings concerning vertebrate porin part I was published in 1997, then summarizing early data and reflections regarding the molecular structure of vertebrate voltage-dependent anion-selective channels, VDAC/eukaryotic porin, and the extra-mitochondrial expression pattern of human type-1 VDAC. Meanwhile, endeavors of different laboratories confirmed and widened this beginning by encircling the function of the channels. Regarding the function of mitochondrial outer membrane-standing VDACs the channels are established parts of the intrinsic apoptotic pathway and thus therapeutic targets in studies on several diseases: cancer, Alzheimer's disease, Down Syndrome, Parkinson's disease, Amyotrophic Lateral Sclerosis, cystic fibrosis and malaria. Regarding cell membrane-integrated type-1 VDAC it has been documented by different approaches that this porin channel is engaged in cell volume regulation, trans-membrane electron transport and apoptosis. Furthermore, new data insinuate a bridging of extrinsic and intrinsic apoptotic pathways, putatively gaining relevance in Alzheimer research. Mammalian type-1 VDAC, a β-barrel, is basically built up by nineteen β-sheets connected by peptide stretches of varying lengths. The molecule also comprises an N-terminal stretch of some twenty amino acids which, according to biochemical data, traverses the channel lumen towards the cytosolic surface of outer mitochondrial membranes or the plasma lemma, respectively and works as voltage sensor in channel gating. In artificial lipid bilayers VDACs figure as anion or cation-channels, as VDACs are permeable to both cations and anions, with voltage shifts changing the relative permeability. Type-1 VDAC carries several motifs where glycine residues are in critical positions. Motifs of this type, on the on hand, are established nucleotide binding sites. On the other hand, the GxxxG motifs are also discussed as relevant peptide dimerization/aggregation/membrane perturbation motifs. Finally, GxxxG motifs bind cholesterol. Type-1 VDAC shows one such GxxxG motif at the proximal end of its N-terminal voltage sensor while amyloid Aβ peptides include three of them in series. Noteworthy, two additional may be modified versions, GxxxGxG and GxxGxxxG, are found on β-sheet 19 or 9, respectively. Recent data have allowed speculating that amyloid Aβ induces apoptosis via opening type-1 VDAC in cell membranes of hypo-metabolic neurons, a process most likely running over life time – as leaves fall from trees in the tropics – and ending in Alzheimer's disease whenever critical brain regions are affected. The expression of GxxxG motifs on either reactant under consideration is in line with this model of Alzheimer's disease pathogenesis, which clearly differs from the amyloid Aβ cascade theory, and which can, furthermore, be understood as a basic model for apoptosis induction. However, to assume randomly distributed interactions of body wide found amyloid Aβ peptides with the N-terminal voltage sensors of ubiquitously expressed cell membrane-standing human type-1 VDAC opens up a new view on Alzheimer's disease, which might even include a clue on systemic aspects of the disease. While elaborating this concept, my focus was at first only on the GxxxG motif at the proximal end of the N-terminal voltage sensor of type-1 VDAC. Here, I include a corresponding sequence stretch on the channel's β-sheet 19, too.

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1. Introduction

Much progress has been made on VDAC/eukaryotic porin since 1997, when "New findings concerning vertebrate porin" was published [1]. We then summarized our initial data on the primary structure of a human VDAC preparation [2,3], later on called type-1 VDAC, and on its extra-mitochondrial expression in the plasma lemma of B-lymphocytes [4], which had been published since 1989, together with corresponding reports from different laboratories on either issues. The channel represents the product of the gene locus VDAC1 on human chromosome 5, and our early work on it, meanwhile, turned out to be a rather seminal factor concerning molecular VDAC research.

Here the focus is 1.) on our endeavors to experimentally define the function of cell membrane-standing vertebrate, predominantly mammalian, type-1 VDAC which ended in the demonstration that monoclonal mouse antibodies raised against human type-1 VDAC (Porin 31HL), as well as the anion channel blocker DIDS, abolish the regulatory volume decrease (RVD) of HeLa cells [5]. These data are in line with results of different laboratories concerning this problem, which is of rather high cell physiological relevance. There are recent reviews summarizing the pros and also the pitfalls in this exciting story [6–8]. However, evidence points to type-1 VDAC as forming the channel part of volume regulated anion channels (VRACs) which play a critical role in cell volume regulation and thus apoptosis. Noteworthy, additional recent reviews deal with varying aspects of VDAC and emphasize research on the channel [9–17]. And 2.) I summarize my recent reflections on the putative relevance of the GxxxG motif on the N-terminal voltage sensor of human type-1 VDAC, and on a corresponding form on β-pleated sheet 19, too. Finally, I propose to pay credit to other sequence stretches of the channel including critical glycine residues.

Concerning molecular structure, the channel has been shown to be a β-barrel carrying an additional N-terminal stretch of some twenty amino acids that works as a voltage sensor. This critical channel part in positions 20 to 24 of the native molecule shows just one GxxxG motif [1–3] while amyloid Aβ peptides, cut from the amyloid precursor protein (APP) and found in several body fluids of healthy and Alzheimer people or Alzheimer plaques, respectively, comprise 24 to 42 building blocks including three GxxxG motifs in series [18]. However, it represents just one type of motifs carried by VDAC where glycine residues are in critical positions. Additional variants: GxxxS, GxG, GxS and GxxxGKST are deemed as nucleotide binding sites [19] while GxxxG motifs are discussed in a twofold way. Research on GxxxG sequence motifs has started in the early nineties of last century by ethidium binding studies [20] and soon entered the protein field [21]. Meanwhile, the motifs play their role in studies on membrane proteins, this in the context of 1) peptide dimerization/aggregation/membrane perturbation studies or 2) ATP- and cholesterol-binding, respectively [22–26]. However, the molecular size of the reactants under discussion appears to fit putative interactions.

Outer mitochondrial membrane-incorporated VDAC channels have been discussed in the context of the intrinsic apoptotic pathway since the 1990s [27]. More recent data on a function of plasma membrane-standing type-1 VDAC in apoptotic volume regulation [28] and on cisplatin binding of VDAC [29] made me ask if type-1 VDAC in the plasma lemma might work in the extrinsic apoptotic pathway, too [30–32]. From here, the stimulating results of a recent study by XM Zhang et al. (2010) [33] could be read as pointing in this direction [34,35]. The authors, remembering cerebral hypo-metabolism and amyloid accumulation as the prevailing neuropathological characteristics of Alzheimer's disease, started to define the effects of neuronal hypo-activity on amyloid plaque genesis in the Tg2576 transgenic mouse model of Alzheimer's disease. What they found was that unilateral naris-occlusion resulted in an elevation of the β-secretase BACE1 in neuronal terminals of deprived bulb and piriform cortex of young adult mice. Furthermore, locally increased BACE1 immunoreactivity was correlated to amyloid deposition. In their conclusion the authors suggested that functional deprivation or neuronal hypo-activity facilitates amyloid plaque formation in the forebrain of Tg2576 mice [33].

To conclude, the putative voltage sensor of mammalian type-1 VDAC, ubiquitously expressed in outer mitochondrial membranes, endoplasmic reticulum, outer nuclear membrane and plasma lemma, carries one single GxxxG motif while amyloid Aβ peptides, body wide found in blood and liquor, show three of them in series. Glycine motifs of similar structure are found on β-pleated sheets 9 and 19 of the channel. Following the idea that amyloid Aβ peptides might figure as openers of cell membrane-integrated human type-1 VDAC and thus induce apoptosis on cells critical in the pathogenesis of Alzheimer's disease, meanwhile, resulted in additional consideration, worth to keep in mind in the field.

2. Basic data concerning VDAC in the plasma lemma

2.1. Molecular structure and gating of VDAC

Molecular research on VDAC channels in the animal kingdom started in 1989 with the elaboration of the complete primary structure analysis of human Porin 31HL, i.e. human type-1 VDAC, the gene product of VDAC1 on chromosome 5. To achieve, the native channel active molecule had been purified from highly enriched cell membrane preparations of the established B lymphocyte cell line H2LCL via solubilization in the detergent Nonidet P40 and two steps of classical ion-exchange chromatography [4] and sequenced by Edman degradation. Accordingly, the native molecule includes 282 amino acids, its N-terminal alanine being acetylated. Concerning secondary structure, the peptide chain appeared to be arranged in an N-terminal α-helical stretch of some twenty amino acid building blocks followed by a series of peptide stretches of putative β-pleated sheet structure interconnected by peptide bridges of varying lengths [2]. To notify, a study starting with highly enriched mitochondria again from the H2LCL cell line proved the molecular identity of human cell membrane-derived and outer mitochondrial membrane-derived human type-1 VDAC [3].

This breakthrough paved the road for many VDAC analyses to follow. Primary structure analyses quickly moved over to the DNA level resulting in e.g., elaboration of many VDAC primary structure analyses from different sources, detection of VDAC isotypes and the development of recombinant expression systems finally allowing three-dimensional structure analyses of mammalian type-1 VDAC [36–45]. In mammals three VDAC isotypes have been found, concerning crystal structures data on recrystallized human and mouse type-1 VDAC were published in 2008. Recent endeavors to refine knowledge concerning the N-terminal voltage