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Reflections on VDAC as a voltage-gated channel and a mitochondrial regulator

Carmen A. Mannella · Kathleen W. Kinnally

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Abstract There is excellent agreement between the electrophysiological properties and the structure of the mitochondrial outer membrane protein, VDAC, ex vivo. However, the inference that the well-defined canonical "open" state of the VDAC pore is the normal physiological state of the channel in vivo is being challenged by several lines of evidence. Knowing the atomic structure of the detergent solubilized protein, a long sought after goal, will not be sufficient to understand the functioning of this channel protein. In addition, detailed information about VDAC's topology in the outer membrane of intact mitochondria, and the structural changes that it undergoes in response to different stimuli in the cell will be needed to define its physiological functions and regulation.

Keywords VDAC · Mitochondrial porin · Patch clamp · Planar bilayer · Channel · Mitochondria

Introduction

The first paper describing the voltage-gated ion channel activity found in detergent extracts of mitochondrial outer membranes by Schein et al. (1976) was published over 30 years ago. Most early papers about VDAC focused on its interesting and, in some ways, puzzling electrophysiological characteristics when inserted in planar lipid bilayers. That this 30-kDa protein might form thousands of pores in each mitochondrion's outer membrane (extrapolated from the bilayer results) neatly explained the high permeability of the membrane inferred from its osmotic unresponsiveness in, and the rapid rates of respiration of, isolated intact mitochondria, as well as the porous appearance of outer membranes in electron micrographs. At the same time, however, it was not obvious what to make of the voltage-gating phenomenon. When inserted in bilayers, VDAC tends to be open (conductance (g) $g \sim 650$ pS at 150 mM KCl) at zero transmembrane potentials and to partially close ($g \sim 300$ pS) with relatively small voltages of either polarity (De Pinto et al. 1987; Pavlov et al. 2005; Schein et al. 1976; Zizi et al. 1994). Several lines of experimentation indicated that this partial closure involves a major conformational change in the protein, with movement of one or more pore-forming regions out of the membrane (Peng et al. 1992; Thomas et al. 1993). That VDAC's ion conductance could be modulated in vitro suggests that the channel might regulate overall mitochondrial function in vivo, by controlling outer membrane permeability to metabolites. However, since even the partially closed state of the channel is large enough to instantly collapse any transmembrane ion gradients, it would seem to be impossible to close the channel in mitochondria by the mechanism employed in bilayer experiments. Thus, the question was raised whether the electrical gating observed in vitro has any relevance to in-vivo regulation of outer-membrane permeability or whether it represents a phenomenon peculiar to an artificial bilayer environment.

This paper re-examines VDAC's in-vitro characteristics as a voltage-gated ion channel, and attempts to reconcile them with evidence regarding the protein's presumed in-vivo role as gatekeeper for entry and exit of mitochondrial metabolites.

C. A. Mannella
Resource for Visualization of Biological Complexity,
Wadsworth Center,
Albany, NY 12201-0509, USA

K. W. Kinnally (✉)
Department of Basic Sciences,
New York University College of Dentistry,
New York, NY 10010, USA
e-mail: kck1@nyu.edu

VDAC's membrane crystal structure: compatibility with planar bilayer conductance

Electron microscopic studies by Parsons and colleagues in the 1960s provided the earliest indications that the mitochondrial outer membrane contains numerous pores. The plant membrane was found to contain random, close-packed arrays of negative-stain-filled "pits", roughly 3 nm in diameter (Parsons et al. 1965). Years later, ordered arrays of similar stain-accumulating loci were observed in outer membranes from fungal mitochondria (Fig. 1a), and shown to be composed of the protein responsible for VDAC activity by antibody labeling (Mannella 1982; Mannella and Colombini 1984). Determination of the three-dimensional structure of VDAC in these mitochondrial outer membrane arrays was made possible by the discovery that gradual lipid depletion (by phospholipase) improved the frequency, size and quality of the crystalline regions (Mannella 1984). In the highest resolution (1.3 nm) projection maps of the membrane crystals embedded in gold–glucose—which provides a more water-like environment from the perspective of H-bonding than the metal salt solutions commonly used as negative stains—the projected diameter of the pore measures ~2.0 nm (Verschoor et al. 2001). Combining projections from multiple, tilted membrane crystals, the three-dimensional structure of VDAC, or more properly of its gold-filled pore and opposing membrane surfaces, was obtained at 1.8 nm resolution, revealing a roughly circular lumen with notches at either end (Fig. 1b) (Guo et al. 1995). This topology is consistent with that of bacterial porins formed by cylindrically folded β-sheets (β-barrels), in which some transmembrane β-strands extend further than others due to their length and/or tilt relative to the membrane plane (Popp et al. 1996; Mannella 1997). The projected density map of the VDAC protein itself was obtained at a resolution of 1.8 nm by correlation averaging of the unit cells in membrane crystals suspended in amorphous ice without any heavy metals (Guo and Mannella 1993; Mannella 1989). The density maps show features in the VDAC lumen consistent with those in the 3-D reconstruction, such as lower protein density at the notch regions, and yielded a precise diameter for the Cα backbone of the β-barrel: 3.8±0.2 nm. This parameter provides an important constraint for modeling and is consistent with a pore lumen diameter of 2.0–2.5 nm, allowing for space-filling by amino acid residues inside the lumen. Subsequent measurements of the VDAC pore opening by electron microscopy of metal-shadowed VDAC arrays (Dolder et al. 1999; Thomas et al. 1991) and, most recently, by atomic force microscopy (AFM) of hydrated membranes (Goncalves et al. 2007) are in agreement with the pore diameter determined 19 years ago. AFM is better than cryo-electron microscopy at detecting the protruding protein domains that border the notches in the pore lumen, but cannot fully image the pore interior since the probe can only reach about half-way into the lumen.

Interestingly, there is also good agreement between the physical dimension of the pore in the mitochondrial outer membrane and that inferred from the size of the conductances detected when detergent-extracted VDAC protein inserts into planar phospholipid bilayers. The conductance of the canonical open state of bilayer-inserted fungal VDAC is 645 pS (in 150 mM salt) (Fig. 2). The inner diameter (bore), *d*, of an ideal cylindrical ion channel can be estimated knowing the resistivity of the ion solution, and the pore's access resistance and length (Hille 2001). The

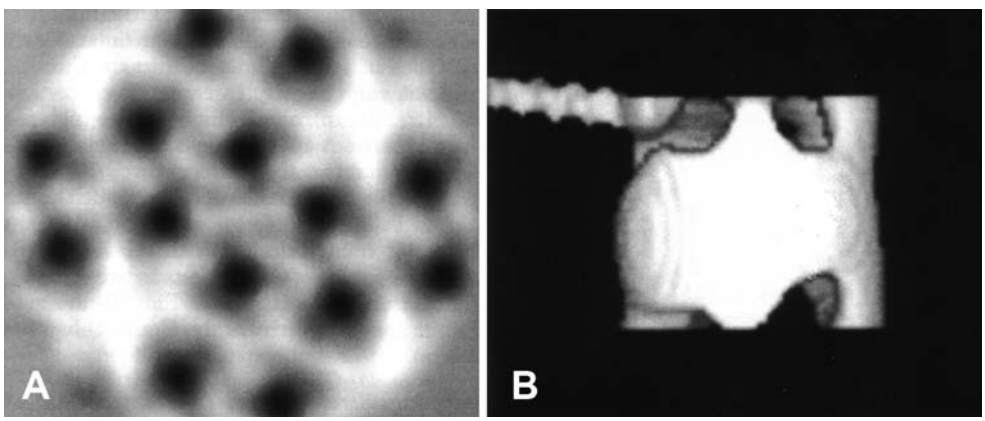
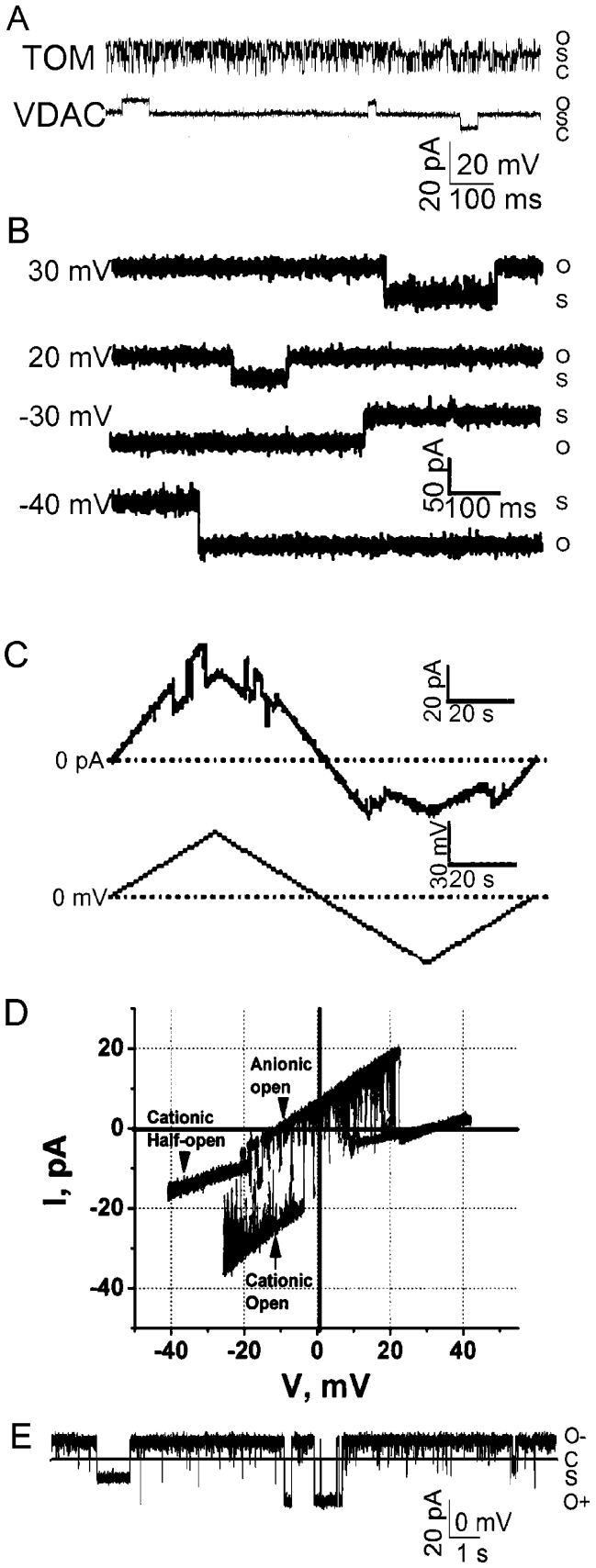


Fig. 1 Structure of VDAC in the mitochondrial outer membrane. **a** A typical crystalline array of VDAC pores induced by lipid depletion in outer membranes isolated from fungal mitochondria. This membrane was embedded in aurothioglucose (glucose with a single gold-atom covalently bound), imaged by low dose electron microscopy and analyzed by correlation averaging. Each gold-filled (*black*) pore is 2-nm in diameter. The empty (*white*) spaces at the four corners around the central group of six pores are the sites of binding of antibodies against the N-terminal of the polypeptide. **b** The model of membrane-bound VDAC obtained by 3-D reconstruction, showing the inferred orientation of the N-terminal α-helix (described in text). Figure modified from data presented in Guo et al. (1995) (with permission from Elsevier Limited)



◀ **Fig. 2** Electrophysiological studies of VDAC. **a** Current traces of single VDAC and TOM single channels at 20 mV obtained by patch clamping proteoliposomes containing mitochondrial outer membranes of mouse FL5.12 cells. Media was symmetrical 150 mM KCl, 5 mM HEPES pH 7.4. Current traces were low pass filtered at 2 with 5 kHz sampling. *O*, *S*, and *C* indicate open, half-open substate, and closed conductance levels. **b**, **c** Current traces at the indicated voltages (**b**) of a planar bilayer containing two VDAC from *Neurospora crassa* outer membranes. Current trace (*upper trace* in **c**) in response to voltage ramping in the range ±50 mV (*lower trace* in **c**) is shown. Media was symmetrical 150 mM KCl, 5 mM $CaCl_2$, 5 mM HEPES, pH 7.4. **d**, **e** VDAC has a cation- and an anion-selective open state. *I–V* curve (**d**) and current trace at 0 mV (**e**) of a single *Neurospora crassa* VDAC in a membrane patch excised from a proteoliposome. For ion selectivity measurements in panels (**d**) and (**e**), the media in the pipette was 150 mM KCl, 5 mM HEPES (pH 7.4) and in the bath was 30 mM KCl, 184 mM mannitol, 56 mM sucrose, 5 mM HEPES (pH 7.4). Conductance is proportional to slope in *I–V* curves. Note the presence of two fully open states with different selectivity and a half-open state with cation selectivity. The current trace at 0 mV illustrates transitions between the open anion-selective (*O*−), open cation selective (*O*+), and half-open cation-selective (*S*, substate) states. The line corresponds to 0 pA and the closed (c) state. Figure modified from data presented in Pavlov et al. (2001, 2005) (with permission from Elsevier Limited)

electrophysiological value for VDAC's bore matches that determined by EM (2.0–2.5 nm) for pore length's=5.5–7 nm, a reasonable range for the thickness of the mitochondrial outer membrane. Other studies that sized VDAC's pore using non-electrolyte polymers report values of similar dimensions (Carneiro et al. 1997; Carneiro et al. 2003). This agreement provides an important albeit partial validation of the bilayer work: *The open-state conductance created by the VDAC protein in an artificial planar lipid bilayer matches the physical size of the VDAC pore in the mitochondrial outer membrane*. Moreover, this finding argues that the conformation of the protein in its native membrane is readily accessible when the protein inserts into lipid bilayers from the detergent micelle state. This might be attributable, in part, to the protein maintaining considerable elements of its native secondary structure in some detergents, such as LDAO, as indicated by circular dichroism (De Pinto et al. 1987; Shao et al. 1996).

The membrane crystals of VDAC are polymorphic, meaning they exhibit multiple lattice types, but changes in packing geometry of the pores do not correspond to large-scale changes in lumen diameter expected for the partial closure seen in bilayers. Of course, this is a case of absence-of-evidence, not evidence-of-absence, since it was not possible to create transmembrane potentials in the unsealed membrane vesicles. Interestingly, a polyanionic modulator that reduces the energy barrier between the fully and partially open states of "bilayer VDAC" had a dramatic effect on the membrane crystals suggestive of a particular conformational change in the mitochondrial form of the protein (Guo and Mannella 1993; Tedeschi and Kinnally 1987). The usual membrane array contains regularly spaced

pore-free regions that specifically bind antibodies against the N-terminal domain of the protein (Guo et al. 1995) (Fig. 1a). This protein domain is predicted to fold as an amphipathic alpha-helix, and so it was suggested that these helices normally extend laterally away from the pore lumen, keeping the pores "at arms length" in these regions (Fig. 1b). The change in pore organization caused by the modulator corresponds to loss of the "pore-free" zones, suggesting that the N-terminal helices have lifted off the membrane surface and no longer extend laterally between the pores. That was remarkable since even binding of the Fab fragment of the N-terminal antibody to "mitochondrial VDAC" did not induce this change in protein packing. However, as noted, the projected size of VDAC's lumen was unaffected by the modulator. It was suggested that the fully open state of VDAC might be stabilized by interaction of the N-terminal domain with the surface of the membrane bilayer and that the modulator might work by weakening this interaction and thereby destabilizing the fully open state of the pore (Guo et al. 1995). Support for this hypothesis was provided by experiments with bacterially expressed recombinant VDAC (Koppel et al. 1998; Popp et al. 1996). Variants of the protein with truncated N-termini tend not to form stable channels in bilayers, whereas variants with N-terminal extensions form normal channels.

Observations of VDAC activity outside planar lipid bilayers

The single channel behavior of VDAC reconstituted in giant liposomes fused with purified outer membranes (in the absence of detergents) and detected with patch clamp techniques shows many of the same characteristics as that of VDAC inserted into planar bilayers from detergent suspension (Fig. 2a–c). Conductance, ion selectivity, and kinetics of VDAC in proteoliposomes and planar bilayers are virtually indistinguishable (Fig. 2b,c). However, the voltage dependence of partial closure of single VDAC channels in liposomes is not as symmetric as in planar bilayers. The voltage at which the probability of partial closure is 0.5, V_0, is smaller for pipette-negative compared to pipette-positive voltages in liposomes (Fig. 2). This suggests an asymmetry in gating behavior that might be retained in membrane–liposome fusion but lost when proteins are inserted into bilayers from detergent suspension.

The first electrical recordings of the native outer membrane were made by applying patch-clamp techniques to isolated mitochondria about 20 years ago (Kinnally et al. 1987, 1989; Mannella and Tedeschi 1987; Tedeschi and Kinnally 1987). The low resistance seals formed in low ionic strength media (10 mM KCl) revealed currents that increased sharply with voltage amplitudes over 40 mV (Kinnally et al. 1989). Although single channel events could not be recorded (due to the low resistance of the seals), the currents could be tentatively attributed to VDAC, at least in part, based on their inhibition by two known VDAC effectors, a synthetic polyanion and succinic anhydride (Tedeschi and Kinnally 1987).

More recent studies of the channel activities of the native outer membrane in either isolated mitochondria or within cells via patch clamping at physiological ionic strength (unlike the 0.5–1 M salt solutions used in most bilayer work) have repeatedly failed to detect single-channel behavior consistent with that observed in patch-clamped liposomes or voltage-clamped planar bilayers (Dejean et al. 2005; Jonas et al. 2004; Moran et al. 1992; Pavlov et al. 2001, 2005; Sorgato and Moran 1993). While 300–350 pS transitions are found at low potentials, these likely correspond to the TOM channel, whose single channel behavior in proteoliposomes and native membranes is almost indistinguishable (Grigoriev et al. 2004; Muro et al. 2003). The TOM channel, like VDAC, is presumably formed by β-barrels and so it might be surprising that their responses to bilayer reconstitution are so different. One very real possibility is that VDAC in the native mitochondrial outer membrane is strongly regulated by other proteins, which are lost during reconstitution. Possibilities include an as yet unidentified endogenous modulator in the mitochondrial inter-membrane space (Holden and Colombini 1988, 1993; Xu et al. 2001; Zizi et al. 1994), Bcl-2 family proteins (see below), and tubulin (Rostovtseva et al. 2008). Tubulin has been reported to facilitate full closure of VDAC, allowing the formation of tight gigaseals on the outer membranes of isolated and cellular mitochondria. The implication, of course, is that VDAC is normally fully closed in isolated mitochondria and within cells. If so, then the large open pores observed in membrane arrays and in bilayers would represent a protein conformation that is more easily accessible (energetically favored) when the protein is *not* in intact mitochondria. It should be noted here that there is one condition in which VDAC reconstituted from detergent micelles into lipid bilayers undergoes complete but reversible closure, namely exposure of VDAC-containing liposomes to pH 5.5. This same condition causes reversible decrease in the β-sheet content of the VDAC polypeptide in LDAO micelles (Shao et al. 1996). *Might this lower β-sheet, fully (not partially) "closed" conformation be the usual state of the VDAC polypeptide under physiological conditions in the cell?*

Canonical partial closure of VDAC reconstituted in bilayers is accompanied by a reversal in selectivity from slightly anionic to slightly cationic (Fig. 2). The accepted explanation for this coupling between conductance size and ion selectivity of the pore is that the conformational change

associated with partial closure involves major polypeptide rearrangements that change the balance of fixed positive and negative charges in the pore lumen. Recently, (Pavlov et al. 2005) reported that VDAC is capable of reversing its ion selectivity without significantly modifying the magnitude of its ion conductance (i.e. pore lumen diameter), as shown in Fig. 2d and e. This finding demonstrates that a major structural rearrangement is not requisite for VDAC to switch between anion- and cation-selective states and suggests that VDAC might have one or more "selectivity gates", local mobile structural features that can have a large influence on ion flow. Movement of structural domains such as the N-terminal α-helix or the "flap" in or around the pore lumen might represent examples of such gates e.g., (Mannella 1998). In this context, it is worth recalling that the ion selectivity of patches of native outer membrane are routinely cation selective (Pavlov et al. 2001, 2005) suggesting that the more common "open" state of VDAC in the membrane (as opposed to artificial liposomes) might be either the partially closed state or the higher conductance cation-selective state of Pavlov et al. (2005).

Involvement of VDAC in regulation of mitochondrial function

The VDAC protein has many putative functions in terms of mitochondrial metabolite transport and volume regulation, and apoptosis. However, the above results suggest that old concepts about this channel-protein's normal permeability state in the cell may need re-thinking. This is further amplified by current controversies regarding the channel's role in apoptosis.

VDAC presumably regulates the mitochondrial influx and efflux of metabolites such as substrates for oxidative phosphorylation and ATP. Rostovtseva and Colombini (1996) showed that the cationic partially closed state of VDAC in bilayers is less permeable to ATP. Colombini's group showed that ADP diffusion is more limiting for mitochondrial oxygen consumption in the presence of VDAC modulators which favor the channel's partially closed state (Holden and Colombini 1988, 1993; Liu and Colombini 1992; Liu et al. 1994). Likewise, knockout studies done both in yeast and mouse embryonic fibroblasts by the Forte, Colombini and Craigen laboratories have shown the importance of VDAC in regulating respiration and overall metabolism (Ahmadzadeh et al. 1996; Blachly-Dyson et al. 1993; Forte et al. 1996; Sampson et al. 1996). Ironically, as discussed in the previous section, it is likely that the majority of VDAC pores in intact mitochondria are usually in a fully closed conformation, and that the physiologically permeability of the mitochondrial outer membrane may be determined by an ensemble of a relatively small number of predominantly cation-selective pores, including VDAC in its canonical "partially closed" state and in its newly discovered larger conductance cation-selective state, and perhaps the TOM channel. This means so-called modulators that favor the canonical "partially closed" state of VDAC's pore might not be acting to close VDAC but to open it! This makes ultimate understanding of the multitude of permeability states that the VDAC protein occupies under different physiological conditions *in the cell* all the more important.

Contrary to conclusions from experiments that suggest that VDAC might be required for cytochrome c release from mitochondria during apoptosis (Shimizu et al. 2000a, 2000b, 2001; Tsujimoto and Shimizu 2000), more recent experiments indicate that VDAC is dispensable for this process (Baines et al. 2007; Galluzzi and Kroemer 2007; Krauskopf et al. 2006). However, there is evidence that an isoform of VDAC (VDAC2) plays a principal role in suppressing apoptosis in mice by sequestering Bak, which would otherwise oligomerize to form the channel through which cytochrome c is released, called MAC (mitochondrial apoptosis-induced channel). Thus, VDAC2 knock-out increases susceptibility of MEF cells to apoptosis (Cheng et al. 2003). The apoptosis-preventing activity of Bcl-xL has been linked to VDAC by a mechanism related not to cytochrome c release but to the channel's metabolite permeability. There is evidence that Bcl-xL enhances occupation of the canonical fully open state of VDAC, which by inference would enhance metabolite permeability and ATP generation, and, it is argued, prevent apoptosis in FL5.12 cells (Vander Heiden et al. 2001). Furthermore, Jonas' group has reported that VDAC expression is required for the intracellular action of truncated BCL-xL on mitochondrial channel activity (Jonas et al. 2004). In contrast, VDAC tightly binds hexokinase in some glycolytic cancer cells, which is reported to decrease VDAC conductance and the resulting decrease in outer membrane permeability is said to suppress apoptosis (Campbell and Chan 2007). Whether increasing or decreasing VDAC permeability in the cell supports or prevents apoptosis is obviously an unsettled issue, likely clouded by the fundamental lack of knowledge about VDAC's normal physiological conformation on the mitochondrial surface and its regulation *within the cell*.

Future directions and conclusions

Despite the collective efforts of several labs over the last 20 or so years, there is still no atomic-level structural model for the protein that forms VDAC. But, while such a structure will inevitably be useful and illuminating, it is more likely to fire up new controversy than end debate

about the physiological functions of VDAC. As noted above, VDAC is a versatile performer, able to do things in synthetic lipid bilayers that may or may not reflect what it does in its native membrane environment—and vice versa. How much confidence will biologists have in the physiological significance of an atomic structure determined, say, by X-ray crystallography or multi-dimensional NMR studies of the protein in a detergent environment? Complicating matters further is the fact that there may not be currently sufficient consensus data about the topology of the VDAC protein in its native environment of the outer membrane to validate any detergent-derived model provided by structural biology in the near future (De Pinto 2008; De Pinto et al. 1993; Stanley et al. 1995).

Ironically, the early excellent agreement between the physiological and structural properties of the VDAC protein ex vivo may have served to lure researchers into misconceptions or oversimplifications about VDAC's role in mitochondrial function. The fact is that much remains to be learned about its cellular functional states and how they are regulated by small ligands (such as nucleotides, not discussed) and by proteins such as kinases, the Bcl-2 family, and the cytoskeleton. The experimental challenges involve devising in situ probes that can directly and reliably report VDAC's structural and functional states under normal physiological conditions and during those special processes, such as apoptosis, that are critically important to understanding disease and to drug discovery.

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