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Biophysical studies reveal lipid-modulated mitochondrial membrane protein thermodynamics

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Integral membrane proteins in eukaryotes adapt to changes in the thickness, fluidity and lateral pressure of their membranous environment by modulating their dynamicity and stability. Interestingly, unlike helical proteins that form intra-strand H–bonds, transmembrane β-barrels require inter-strand H–bonding that is vital to stabilize the lipid– and water–solvated β-barrel scaffold. These β-barrel proteins are exclusively found in the outer mitochondrial membrane, and are indispensable for regulating cellular homeostasis, cellular energetics, and cell survival. In particular, the voltage-dependent anion channels (VDACs) are the metabolite flux proteins of the outer mitochondrial membrane, and these β-barrel proteins respond to alterations in the cardiolipin, cholesterol, and phospatidylglycerol levels in the mitochondrial membrane by regulating its function. Additionally, VDACs are also structurally unique as they possess 19 transmembrane β-strands, with the 1^{st} and 19^{th} strands stabilized by parallel H–bonding. What is not understood is how this 19-stranded scaffold responds to substantial changes in the mitochondrial lipidic environment. It is also not known how VDACs carry out their various auxiliary functions in the cell (regulation of hexokinase, α-synuclein, Bax, BAK, tBid, modulating peroxide and superoxide levels in the mitochondrial intermembrane space, assisting protein import into mitochondria) in addition to their primary role as voltage-regulated ATP, ADP, NADH, NAD^+, Ca^{2+} transporters.Past studies question the molecular basis for structure–function regulation of VDAC in mitochondria, the biological relevance of an odd-stranded β-barrel, and its lipid-mediated homo- and hetero-oligomerization. We address this conundrum by presenting the first experimental evidence for how the lipid membrane modulates the thermodynamic stability and function of human VDACs. We identify an evolutionary, structural, and functional significance for the 19-stranded scaffold and the parallel H–bonding in its adaptation to cholesterol and cardiolipin level–mediated thermodynamic regulation, while also effectively carrying out its function of metabolite flux in a voltage-regulated manner.