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Abstracts

S6 VDAC

Lectures

6L.1 Characterization of human VDAC isoforms: A peculiar function for VDAC3?

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VDACs are a family of pore-forming proteins mainly located in the mitochondrial outer membrane. In mammals three isoforms exist. In this work we have compared the human VDACs transformed in a yeast strain lacking the endogenous porin. VDAC1 and 2 are able to complement the lack of porin in mitochondrial respiration and modulation of ROS. VDAC3 has a limited ability to support the mitochondrial respiration and has no influence in the control of ROS production. The over-expression of VDAC isoforms in wild type yeast strain led to a dramatic sensitivity to oxidative stress, especially for VDAC3, and a shorter lifespan in respiratory conditions. Real-time PCR comparison of the isoforms indicated that in HeLa cells VDAC1 is 10 times more abundant than VDAC2 and 100 times than VDAC3. The over-expression of any single isoform caused a 10 time increase of the transcripts of VDAC2 and VDAC3, while VDAC1 is not changed by the overexpression of the other isoforms. Models of VDAC2 and VDAC3 isoforms structure showed that they could be made of a 19-strands b-barrel and an N-terminal sequence with variable features. In this work we show for the first time a functional characterization of VDAC3 in a cellular context.

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6L.2 Structure and function of the voltage dependent anion channel

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The voltage-dependent anion channel (VDAC) is the main pathway for metabolites, small molecules and ions across the outer mitochondrial membrane. A large amount of functional data has been accumulated in over 30 years of VDAC research, but the lack of a three-dimensional structure has made an understanding of VDAC function essentially impossible. This situation has changed recently, as high-resolution structures of VDAC were determined [1–3]. Here, we elucidate functional aspects of VDAC on the background of the three-dimensional NMR structure of human VDAC-1 in LDAO micelles [1] as well as on new experiments. The main part of the VDAC polypeptide chain forms a 19-stranded beta-barrel, with only the N-terminal 25 residues not being part of the barrel architecture. The dynamic properties of this N-terminal segment were determined by solution NMR spectroscopy, providing a link to the well-known voltage gating process. Further, the VDAC binding sites for the metabolite NADH and the natural ligand cholesterol were characterized structurally. We can also link our results to the native state of VDAC. The entire outside perimeter of the barrel is hydrophobic and covered by detergent molecules, compatible with the membrane bilayer topology. The inner diameter of the VDAC-1 pore is about 25 Å, consistent with published micrographs of native and native-like preparations. NMR spectroscopy and electron microscopy studies of VDAC in lipid bilayer nanodiscs provide a new means to connect micelle-bound VDAC structurally and functionally to its native state [4].

References

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6L.3 Communication between mitochondria and nucleus: Putative role for VDAC in reduction/oxidation mechanism

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Voltage dependent anion channel (VDAC) was identified in 1976 and since that time has been extensively studied. It is well known that VDAC

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