

Gene Section

Review

VDAC1 (voltage-dependent anion channel 1)

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Identity

Other names: PORIN, VDAC-1

HGNC (Hugo): VDAC1

Location: 5q31.1

DNA/RNA

Description

The gene encompasses over 33 kb of DNA; 9 exons.

Transcription

There are 3 splice variants reported but they all encode the same 282 amino acids protein.

One transcript variant has an mRNA product length of 1993 bp (accession number: NM_003374). Processed length 852 bp.

Protein

Description

Voltage-dependent anion-selective channel protein 1 (VDAC1, accession number: NP_003365.1) encodes for a protein product length of 283.

VDAC1 regulates the flux of mostly anionic metabolites through the outer mitochondrial membrane, which is highly permeable to small molecules.

VDAC is the most abundant protein in the outer membrane.

Changes in membrane potentials can switch VDAC between open or high-conducting and closed or low-conducting forms.

Expression

Mitochondrial porins have been found in all eukaryotic cells studied to date.

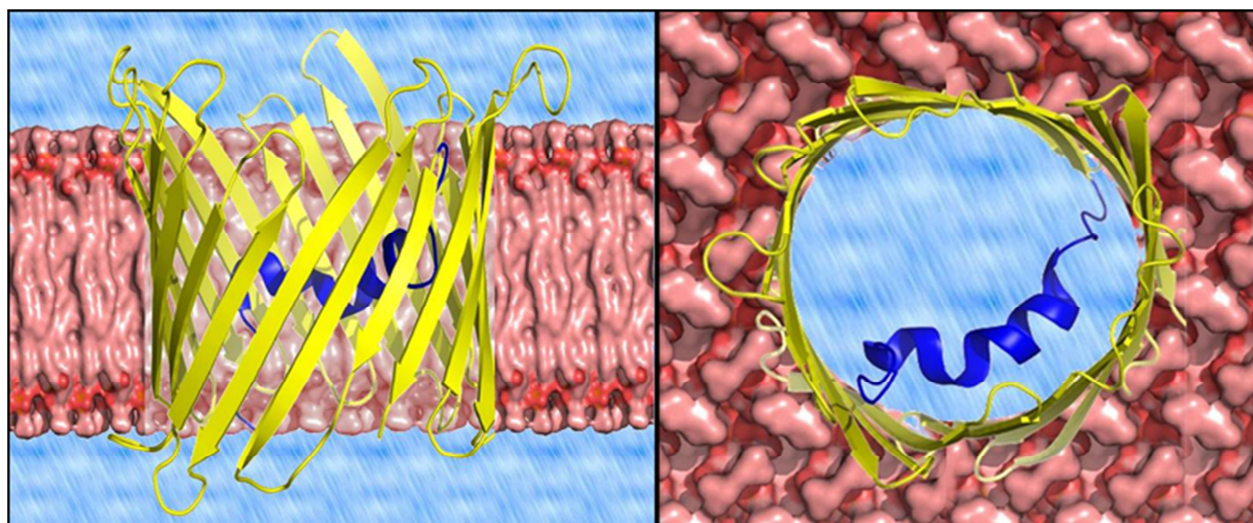
In mammalian tissues VDAC1 is expressed in many normal and tumour tissues.

It has been well characterized in brain, heart, skeletal muscle, and liver.

Human cancer cell lines express higher VDAC1 levels than normal cells (Shinohara et al., 2000; Sinamura et al., 2006; Sinamura et al., 2008).

Localisation

Primarily in the Outer Mitochondrial Membrane (OMM), but in erythrocytes cell death events (eryptosis) it has been found in the plasma membrane (Sridharan et al., 2012).



Schematic representation of VDAC1 inserted in the membrane. The image was prepared using the crystal structure of mouse VDAC1, PDB ID 3emn (PDB).

Function

VDAC1, located at the OMM, is a key protein in regulating the exchange of ions, nucleotides and a variety of metabolites in and out of the mitochondria. As such, VDAC1 serves a crucial role in cellular energy maintenance. It provides a permeation pathway for metabolites and mobile ions between the cytosol and mitochondria. VDACS are also involved in cell death by interacting with apoptotic proteins and releasing apoptotic metabolites to the cytosol.

Protein modifications. VDAC1 has been shown to be phosphorylated in multiple sites: serine, threonine, and tyrosine. Some candidate kinases have been suggested: GSK3, CaM-II, CKI, PKA, PKC, cdc2, p38MAPK, Nek1, EGFR, and SRC. Following reconstitution of VDAC1 into planar lipid bilayers, phosphorylation by PKA reduces the channel current. In rat liver OMM the N-terminal methionine from VDAC1 is removed and the new amino terminal alanine is acetylated. Two separate studies demonstrated that VDAC1 was multiply acetylated in mouse liver, each study reported different sites. VDAC1 is ubiquitinated following mitochondrial depolarization (Narendra et al., 2010).

Protein interactions. Localization of VDAC1 to the OMM makes it a functional anchor point for molecules that interact with the mitochondria. VDAC1 displays binding sites for glycerol kinase, hexokinase (HK), creatine kinase, mitochondrial creatine kinase (MtCK) (interacts with VDAC1 competing with HK and Bax). VDAC also forms complexes with other proteins, such as the ANT, the peripheral benzodiazepine receptor (TSPO), tubulin, the dynein light chain, mtHSP70, the ORDIC channel, glyceraldehyde 3-phosphate dehydrogenase, actin and gelsolin, as well as with apoptosis-regulating proteins, such as members of the Bcl-2 family.

VDAC1 oligomerization. VDAC1 has been shown to

assemble into dimers, trimers, tetramers, and higher oligomeric states in a dynamic process, including the VDAC1 purified from liver mitochondria, recombinant human VDAC, and liver or brain mitochondrion-embedded VDAC1. The supramolecular organization of VDAC1 has also been demonstrated using Atomic Force Microscope. Oligomeric assembly of VDAC1 has been shown to be coupled to apoptosis induction, with oligomerization increasing substantially upon apoptosis induction and inhibited by apoptosis blockers.

N-terminal domain. The N-terminus of VDAC1 is 25 amino acids long, and contains an alpha helix (between residues 5-16). In recently published 3-D structures the N-terminus resides within the pore; independent studies show that it could move out of the pore. The N-terminal α -helical segment is proposed to be involved in channel gating, where it could be acting as the voltage sensor and possibly regulating the conductance of ions and metabolites through the VDAC1 pore. VDAC1-N-terminus is required for apoptosis induction, its interaction with HK-I and Bcl2 has a protective effect against apoptosis (Arbel and Shoshan-Barmatz, 2009).

Homology

In higher eukaryotes, three VDAC isoforms have been characterized: VDAC1, VDAC2 and VDAC3, encoded by three separate genes. VDACS are highly conserved across species. VDAC1 is the most abundant isoform in most cells, being ten times more prevalent than VDAC2 and 100 times more prevalent than VDAC3 in HeLa cells (De Pinto et al., 2010). Recently it was demonstrated that while VDAC1 and VDAC2 are localized mainly within the same distinct domains of the OMM, VDAC3 is mostly distributed uniformly over the surface of the mitochondrion.

Mutations

Somatic

Direct DNA sequencing of colorectal cancer (CRC) and gastric cancer (GC) led to identification of a recurrent VDAC1 mutation. This mutation, c.332delA, leads to a premature stop codon, resulting in truncation of the amino acid synthesis (p.Asn111MetfsX34) and would remove about 60% length of C-terminal VDAC1 protein. The DNA sequencing indicated that the mutation was heterozygous. There was no significant difference of the mutations with respect to the clinicopathologic features of the GC and CRC (Fisher's exact test, $p > 0,05$) (Yoo et al., 2011).

Implicated in

VDAC1 and cancer

Note

Hexokinase (HK) interacts with VDAC to mediate its anti-apoptotic activity. It has been reported that human cancer cell lines express higher VDAC1 levels than normal cells, while mitochondria from malignant tumor cell lines are capable of higher HK binding, thus increasing protection against apoptosis. The HK-VDAC interaction is thought to underlie cell survival and apoptosis regulation by HK.

A) HK bound to VDAC on the mitochondrial surface provides metabolic benefit that offers the cell a proliferative advantage.

B) HK-I and HK-II binding to VDAC1 protects against apoptosis, with their release enabling activation of apoptosis.

C) HK was shown to reduce mitochondrial reactive oxygen species (ROS) generation through an ADP-recycling mechanism. Accordingly, detachment of HK from VDAC1 could lead to increased H₂O₂ generation and release to the cytoplasm, thereby activating cell death.

D) The interaction of HK with VDAC protects against activation of apoptosis by BCL2-associated X protein (Bax) or Bcl-2 homologous antagonist/killer (Bak). Thus, VDAC-bound HK renders cells much more resistant to apoptosis.

Rare mitochondrial encephalomyopathy

Note

Tissue-specific VDAC isoform 1 (HVDAC1) deficiency in human skeletal muscle is responsible for a rare mitochondrial encephalomyopathy, fatal in childhood (Messina et al., 1999).

Neurodegenerative diseases

Note

Protein level changes of VDAC1 in brain of patients with Alzheimer's disease and Down syndrome have been reported (Yoo et al., 2001).

Although evidence supporting a role for VDAC in the pathogenesis of Alzheimer's disease (AD) exists, its precise contribution is unknown. It has been suggested that VDAC may be involved in membrane dysfunction associated with AD neuropathology. The extent of oxidative damage to VDAC was reflected in the increase in nitrated VDAC1 in AD. VDAC modifications may alter VDAC-mediated bidirectional energy fluxes across the mitochondrial membrane. VDAC has been studied in Down's syndrome patients, epilepsy animal models, in dopamine-induced apoptosis, and amyotrophic lateral sclerosis (ALS). The involvement of VDAC in numerous pathological conditions may result from disturbed VDAC function in energy production, metabolite cross-talk between the cytosol and the mitochondria, or apoptosis regulation.

Muscular and myocardial diseases

Note

In a rabbit model for myocardial ischemia and reperfusion, it was demonstrated that the p38 MAPK inhibitor, PD169316, significantly reduced p38-mediated phosphorylation of VDAC1, implicating VDAC1 in myocardial ischemia and reperfusion.

VDAC and reagent toxicity

Note

ROS are known to activate apoptosis. In addition, ROS appears to activate VDAC. Furanonaphthoquinones (FNQs) were proposed to induce apoptosis via ROS. The ROS production and the anti-cancer activity of FNQs were increased upon VDAC1 overexpression and decreased upon silencing VDAC1 expression by siRNA.

There are other chemicals that directly interact with and modify VDAC's activity. G3139 (oblimersen), an 18-mer phosphorothioate anti-sense oligonucleotide targeted to the initiation codon region of Bcl-2 mRNA, directly binds and reduces the channel conductance of bilayer-reconstituted VDAC. Avicins represent a novel class of plant stress metabolites that exhibit cytotoxic activity in tumor cells, as well as anti-inflammatory and anti-oxidant properties capable of perturbing mitochondrial function and initiating apoptosis in tumor cells. Fluoxetine (Prozac), a clinically-used antidepressant compound which acts on multiple transporters and channels, enhanced cell proliferation and prevented or enhanced apoptosis in various cell lines. Fluoxetine was shown to interact directly with VDAC and inhibit apoptosis. Cisplatin is a widely used anti-cancer drug which acts by inducing apoptosis. Cisplatin binds and modulates VDAC's activity (Yang et al., 2006) to modulate VDAC1 activity. Acrolein (2-propen-1-al), the most reactive of the α,β -unsaturated aldehydes and a toxic compound. VDAC was recently identified as a selectively oxidized target in the AD brain, being significantly carbonylated by acrolein. Endostatin (ES) has been shown to promote the

permeability transition pore (PTP) opening via VDAC. Silencing VDAC1 expression by siRNA attenuates ES-induced apoptosis, while overexpression of VDAC1 enhances the sensitivity of endothelial cells to ES.

References

Messina A, Oliva M, Rosato C, Huizing M, Ruitenbeek W, van den Heuvel LP, Forte M, Rocchi M, De Pinto V. Mapping of the human Voltage-Dependent Anion Channel isoforms 1 and 2 reconsidered. *Biochem Biophys Res Commun.* 1999 Feb 24;255(3):707-10

Shinohara Y, Ishida T, Hino M, Yamazaki N, Baba Y, Terada H. Characterization of porin isoforms expressed in tumor cells. *Eur J Biochem.* 2000 Oct;267(19):6067-73

Yoo BC, Fountoulakis M, Cairns N, Lubec G. Changes of voltage-dependent anion-selective channel proteins VDAC1 and VDAC2 brain levels in patients with Alzheimer's disease and Down syndrome. *Electrophoresis.* 2001 Jan;22(1):172-9

Simamura E, Hirai K, Shimada H, Koyama J, Niwa Y, Shimizu S. Furanonaphthoquinones cause apoptosis of cancer cells by inducing the production of reactive oxygen species by the mitochondrial voltage-dependent anion channel. *Cancer Biol Ther.* 2006 Nov;5(11):1523-9

Simamura E, Shimada H, Hatta T, Hirai K. Mitochondrial voltage-dependent anion channels (VDACs) as novel pharmacological targets for anti-cancer agents. *J Bioenerg Biomembr.* 2008 Jun;40(3):213-7

Arbel N, Shoshan-Barmatz V. Voltage-dependent anion channel 1-based peptides interact with Bcl-2 to prevent antiapoptotic activity. *J Biol Chem.* 2010 Feb 26;285(9):6053-62

De Pinto V, Guarino F, Guarnera A, Messina A, Reina S, Tomasello FM, Palermo V, Mazzoni C. Characterization of

human VDAC isoforms: a peculiar function for VDAC3? *Biochim Biophys Acta.* 2010 Jun-Jul;1797(6-7):1268-75

Narendra D, Kane LA, Hauser DN, Fearnley IM, Youle RJ. p62/SQSTM1 is required for Parkin-induced mitochondrial clustering but not mitophagy; VDAC1 is dispensable for both. *Autophagy.* 2010 Nov;6(8):1090-106

Shoshan-Barmatz V, De Pinto V, Zweckstetter M, Raviv Z, Keinan N, Arbel N. VDAC, a multi-functional mitochondrial protein regulating cell life and death. *Mol Aspects Med.* 2010 Jun;31(3):227-85

Yoo NJ, Park SW, Lee SH. A Frameshift Mutation of the Pro-Apoptotic VDAC1 Gene in Cancers with Microsatellite Instability. *Gut Liver.* 2011 Dec;5(4):548-9

Geula S, Naveed H, Liang J, Shoshan-Barmatz V. Structure-based analysis of VDAC1 protein: defining oligomer contact sites. *J Biol Chem.* 2012 Jan 13;287(3):2179-90

Kerner J, Lee K, Tandler B, Hoppel CL. VDAC proteomics: Post-translation modifications. *Biochim Biophys Acta.* 2012 Jun;1818(6):1520-5

Shoshan-Barmatz V, Ben-Hail D. VDAC, a multi-functional mitochondrial protein as a pharmacological target. *Mitochondrion.* 2012 Jan;12(1):24-34

Sridharan M, Bowles EA, Richards JP, Krantic M, Davis KL, Dietrich KA, Stephenson AH, Ellsworth ML, Sprague RS. Prostacyclin receptor-mediated ATP release from erythrocytes requires the voltage-dependent anion channel. *Am J Physiol Heart Circ Physiol.* 2012 Feb 1;302(3):H553-9

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