VDAC as a Potential Target in Huntingtons Disease Therapy: The State of the Art

Andonis Karachitos, Daria Grobys and Hanna Kmita*

Laboratory of Bioenergetics, Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University in Poznań, Umultowska 89, 61-614 Poznań, Poland

*Corresponding author: Hanna Kmita, Laboratory of Bioenergetics, Institute of Molecular Biology and Biotechnology, Faculty of Biology, Adam Mickiewicz University, Umultowska 89, 61-614 Poznań, Poland; Tel: +4861 829-5901; E-mail: kmita@amu.edu.pl

Rec date: Nov 24, 2015; Acc date: Dec 24, 2015; Pub date: Dec 28, 2015

Abstract

It is becoming increasingly evident that mitochondria dysfunction plays an important role in pathogenesis of Huntington’s disease (HD). However, the underlying mechanism is still needs to be explained. The crucial aspect of the explanation is to indicate the upstream events in mitochondria dysfunction that could contribute to HD. In the review we propose the defect of voltage-dependent anion-selective channel (VDAC), as a causative event in HD-related mitochondria dysfunction. Thus, we propose to consider VDAC as a crucial element in HD etiology and consequently as a reasonable target for therapeutic interventions in HD, based on developing novel therapeutic strategies eliminating mitochondria dysfunction.

Keywords: Huntington’s disease; VDAC; Mitochondria; Therapy

Huntington’s Disease

Huntington’s disease (HD) is a progressive and fatal neurodegenerative disease with a prevalence of about 5-10/100 000. Clinically, the disease is characterized by progressive chorea (involuntary dance-like movements), rigidity, weight loss, dementia, seizures and psychiatric disturbances such as depression, withdrawal and irritability. These symptoms including cognitive deterioration, psychiatric disturbances, and movement disorders result from a selective and continuous loss of neurons from the striatum and deep layers of the cerebral cortex although other brain regions such as thalamus and subthalamic nucleus are also affected [1-3]. Current treatments for HD relieve merely the symptoms and address the control of behavioral symptoms, motor sedatives, cognitive enhancers, and neuroprotective agents [4,5] but are not able to restore neuronal function nor to stop the insidious loss of neurons. As summarized by Kumar et al. [6], although there is an intensive research concerning development of neuroprotective strategies such as fetal neural transplantation, RNA interference (RNAi) and transglutaminase inhibitors (TGaseI), effective therapeutic strategies may not be developed until the next few decades. Thus, a new therapeutic approach involving new potential targets and to start before the symptomatic stage could contribute to HD treatment to be more specific and effective. This, in turn, requires further studies concerning molecular mechanisms underlying HD.

The genetic hallmark of HD is an expansion of an unstable trinucleotide CAG repeat region within the first exon of the gene encoding the protein Huntington (Htt). This results in synthesis of its mutant form (mHtt) containing more than 36 glutamine residues at N terminus although the possible contribution of mHtt encoding mRNA, i.e. toxic mRNA in HD etiology has also been suggested [7]. HD inheritance is autosomal dominant and consequently the prevailing view is that mHtt mediated symptoms result from a toxic gain-of-function mechanism although loss-of-function mechanisms for mHtt and Htt are also proposed [8,9]. Htt is conserved among vertebrates [10], is localized mainly in cytoplasm and exhibits anti-apoptotic properties [11,12]. Importantly, Htt expression in different tissues does not correspond with the restricted distribution of neuropathologic changes in HD [13] but the protein has been shown to be required for mammalian neurogenesis [14]. Its domain model does not indicate any particular functions aside from domains that might mediate protein interactions. Indeed, numerous reports indicate that Htt interacts with above 200 proteins which represent a diverse array of biological functions, including synaptic transmission, cytoskeletal organization, signal transduction, gene expression regulation and metabolism [8,15-17].

Presently available data indicate at the following mechanisms of mHtt toxicity: protein aggregation, excitotoxicity, oxidative stress, impairment of proteolysis and proteasome, enhanced apoptosis and autophagy, transcription regulation, including epigenetic mechanisms and mitochondria dysfunction [6,8,9,18-20]. Although the functional relationship of Htt to mitochondria is still uncertain [21], it is becoming increasingly apparent that mHtt can impair mitochondrial function directly [22]. Moreover, available data indicate that mitochondrial defects may initiate the disease onset [23-31]. Accordingly, the current PubMed searching for “Huntington disease and mitochondria AND review” indicate over 130 review papers addressing mHtt effects on mitochondrial bioenergetics and biogenesis, protein import, complex assembly, fission and fusion, mitochondrial transport including Ca2+ and metal homeostasis, and on the degradation of damaged mitochondria via autophagy (mitophagy). Simultaneously, it is also evident that VDAC (voltage-dependent anion-selective channel), regarded as a dynamic regulator, or even governor, of mitochondrial functions, contributes to affected phenomena directly or by interacting with the involved proteins. The fields of possible interference between the processes impaired within the postulated mechanisms of HD pathogenesis and VDAC-affected processes are shown in Figure 1.
**VDAC as a versatile protein**

The main function of VDAC is metabolite exchange between mitochondria and cytoplasm. Importantly, VDAC gating is currently regarded as the major mechanism of the mitochondrial outer membrane permeability control [32]. Accordingly, as shown in Figure 2, the channel participates in superoxide anion release from mitochondria, ATP rationing, Ca\(^{2+}\) homeostasis, and apoptosis execution [33-36]. Moreover, using Saccharomyces cerevisiae as a model system it has been demonstrated that VDAC mediates the intracellular reduction/oxidation (redox) states and in this way contributes to expression level regulation of different proteins and to communication between mitochondria and the nucleus [37-39]. Thus, VDAC is regarded as a protein decisive for cell life and death [36,40]. Accordingly, the available data suggest that VDAC malfunction may be crucial for Alzheimer disease [41-43], Down’s syndrome [44], epilepsy [45,46] and familial amyotrophic lateral sclerosis [47,48] as well as to cancer [49].

Interestingly, in mitochondria of different organisms VDAC may be present as isoforms encoded by separated genes, displaying different channel-forming activities and playing different roles in cell metabolism and survival [36,40,50,51]. For example, in human mitochondria, as in the case of other vertebrates, three isoforms of VDAC (VDAC1-VDAC3) able to form functional channels have been identified. They are expressed in different tissues and organs at different levels. Translating characteristics of the VDAC isoforms into in vivo functions is still a challenge that may be resolved by application of animal models of VDAC isoform deficiency providing information concerning the isoform-specific functions in cell functioning [52].

Some of these functions depend on their interaction with other proteins in the cytosol and the mitochondrial intermembrane space and are affected by VDAC posttranslational modification, mainly phosphorylation [53]. It has been recently shown for rat VDAC1 that nitrosation not only decreases its conductance but also significantly enhances its appearance in a closed state whereas phosphorylation protects the channel against closing [54]. However, VDAC sensitivity to oxidative modification should not be neglected [e.g., 55]. Accordingly, it has been shown that in the presence of oxidative modification/damage of VDAC the control of the mitochondrial outer membrane permeability might be severely affected leading to mitochondria dysfunction [56-59]. Moreover, the available data suggest that VDAC isoforms may be differently controlled by oxidative modification of cysteine residues. For example it has been shown for human VDAC3 that the cysteine residue modification might be crucial for its channel activity under physiological conditions [60].

The channel properties of VDAC were first reported in 1976 [61] and since that time have been extensively studied [33,36,62]. In a brief, VDAC reconstituted into artificial membranes displays only one fully
open state, which is anion-selective. At higher potentials VDAC exhibits lower conductance and cation-selective states called closed states. However, the channel behavior of reconstituted VDAC is not the same as that of native one located in the mitochondrial outer membrane as several endogenous factors were indicated to modulate VDAC activity, including NADH [63], Ca^{2+} [36], tubulin [64,65], tBid [66] and other members of Bcl-2 protein family [67], hexokinase I and II [36], α-synuclein [68], 18 kDa Translocator protein (TSPO) [69,70] as well as mitochondrial lipids [71] and still unidentified cytoplasmic and mitochondrial proteins [72]. As summarized by [73], VDAC interactions with different proteins contribute to apoptosis, cytoskeleton functions, Ca^{2+} and oxidative-redox homeostasis as well as energy transformation (Figure 2). There are also data pointing at interaction between VDAC and mitochondrial trafficking and fusion/fission machinery [74,75]. Consequently, VDAC modulation may affect processes that are known to be affected by VDAC directly, i.e., the respiratory chain, transcriptional regulation and protein import, Ca^{2+} balance, oxidative stress and apoptosis, or might be affected due to interaction between VDAC and the involved proteins. Thus, conductance of VDAC in living cell needs to be studied in details in order to better understand VDAC function in vivo and effect of VDAC modulators in therapy, including the isoform specificity. However, as mentioned by [76], it is still not clear whether VDAC is intrinsically open in living cells as suggested by the low permeability barrier of the mitochondrial outer membrane or is closed. Therefore, answering the question appears to be important for development of new therapeutic interventions based on VDAC modulators.

VDAC as a therapeutic target

Consistently with the crucial role of VDAC in mitochondrial functioning, VDAC can be regarded as a candidate for effective pharmacological treatment. Taking into account the available data concerning VDAC role in cell life and death [36], the treatment could be based on cytoprotective or cytotoxic strategies. Undoubtedly, impairment of the cell death pathways resulting in their excessive or insufficient activity plays a crucial role in the pathophysiology of several diseases, including cancer, muscular and myocardial diseases as well as neurodegenerative diseases [36,73,77]. However, as mentioned by [73], a given drug interaction with purified VDAC resulting in modulation of its channel activity do not necessarily indicate that this interaction will result in cytotoxicity or cytoprotection. On the other hand, as shown in Table 1, the list of VDAC modulating compounds and affecting cell survival that have been already registered or are during preclinical or clinical trials is not very long.

| Modulator          | Mechanism                  | VDAC Conductance | Cell death                     | Therapeutic potential                  | Clinical status                                                                 | References |
|--------------------|----------------------------|------------------|--------------------------------|----------------------------------------|----------------------------------------------------------------------------------|------------|
| DMA III            | direct interaction         | ND                | Induction                      | chemotherapy to induce apoptosis       | Preclinical                                                                      | [91]       |
| FNQs               | VDAC-dependent ROS production | ND                | Induction                      | chemotherapy to induce apoptosis       | Preclinical                                                                      | [101]      |
| Oblimersen (G3139) | direct interaction         | Block             | Induction                      | chemotherapy to induce apoptosis       | trade name Genasense; over 45 clinical trials including lymphoma and melanoma; still not in clinical practice [89] |
| Methyl jasmonate   | Inhibit HK-VDAC interaction| ND                | Induction                      | chemotherapy to induce apoptosis       | Preclinical; only case report: promising for precancerous and cancerous skin lesions [90] |
| Cisplatin          | direct interaction; human VDAC1 upregulation | ND                | Induction                      | chemotherapy to induce apoptosis       | trade name Cisplatin; chemotherapy and anti-cancer drug; metastasis of tumors located in ovary, testis, bladder as well as head and neck area; still at clinical trials (overall 1928) [73] |
| Erastin            | Inhibit VDAC oligomerization; reduce VDAC permeability to NADH | ND                | Induction                      | chemotherapy to induce apoptosis       | Preclinical                                                                      | [80]       |
| DIDS               | direct interaction, Inhibit superoxide release from mitochondria | Decrease/Inhibition | ND                | Case reports: promising for schizophrenia, psychotic symptoms and bipolar depression** – accordingly, e.g. bipolar disorder depression: 3 trials, phase III and IV; schizophrenia: 6 clinical trials including phase III and IV. [109-112] | Preclinical | [73]       |

Citation: Karachitos A, Grobys D, Kmita H (2015) VDAC as a Potential Target in Huntingtons Disease Therapy: The State of the Art. Pharmaceut Reg Affairs 4: 157. doi:10.4172/2167-7689.1000157
minocycline (7-dimethylamino-6-dimethyl-6-deoxytetracycline) is an antibiotic of the tetracycline family that has multi-faced potential of DIDS has not been defined yet but the rest of the drugs are regarded as potential neuroprotective ones [77,95]. Interestingly, fluoxetine is a potent antidepressant drug, rasagiline (N-propargyl-1-(R)-aminoindan) is an anti-Parkinson drug, also described as drug of various therapeutic approaches for the treatment of Parkinson disease [96,97] whereas minocycline (7-dimethylamino-6-methyl-6-deoxytetracycline) is an antibiotic of the tetracycline family that has multi-faced effects on cell functions and consequently a number of clinical properties including cytoprotective and neuroprotective potency [98,99]. However, a long-term, double-blind, placebo-controlled trial appears highly warranted for definitively establishing the value of minocycline in HD [100].

It should be also mentioned that important part of anti-cancer and neuroprotection strategy including VDAC is silencing or enhancement of the channel expression. For example, it has been shown that overexpression of VDAC1 increases the anti-cancer activity of FNQs, endostatin, cisplatin, mechloroethamine and melphalan [101-103]. Overexpression of VDAC1 has been also reported to shift its equilibrium status towards the oligomer state that is proposed to be crucial for the release of pro-apoptotic proteins from mitochondria resulting in cell death [101,102]. Accordingly, the presence of different cell death modes with overlapping characteristics [104,105] suggests possible VDAC-targeted anti-cancer therapies based on modulation of cell death modes other than apoptosis but the area is still unexplored.

On the other hand, interesting approach in VDAC-mediated anti-cancer therapy has emerged due to observation that interaction of viral proteins with VDAC isoforms can trigger cell death [106]. Neuroprotective strategy may also consist in regulation of VDAC expression. It has been demonstrated that the known neuroprotective activity of asiatic acid (a triterpenoid) may result from its free radical scavenging activity as well as from regulation of VDAC expression at the level of transcription and translation [107]. Moreover, VDAC is also included in development of microRNA-based therapeutics for several neurodegenerative disorders [108].

### Potential role of VDAC in HD

As mentioned above, it is becoming increasingly apparent that mHtt can impair mitochondrial function directly by affecting mitochondrial bioenergetics and dynamics [31]. Undoubtedly, neurons are highly dependent on mitochondria ATP production and Ca\textsuperscript{2+} buffering to maintain excitability, gene expression and synaptic communication, and rely on dynamic trafficking of mitochondria to adapt this limited resource to the variable needs of distant processes in vast neuritic networks. Moreover, neurons require efficient biogenesis and mitophagy to renew or adapt mitochondria levels throughout their lifespan, and proper fusion and fission to allow mitochondria functional and spatial segregation. Thus, distinct mitochondrial roles in neuronal physiology might be affected in HD etiology. Importantly, the affected mitochondria functions include processes that are known to be influenced by VDAC. It has been shown that VDAC contributes to the processes directly or indirectly by interacting with the involved proteins. On the other hand, VDAC may promote cytoprotection including neuroprotection [77,109]. Thus, VDAC may play a central role in mitochondria dysfunction detected in HD (Figure 1) and its attenuation and consequently in HD treatment. However, searching of PubMed provides only two review papers pointing at putative contribution of VDAC to neurodegeneration, including HD [27,46] and one experimental paper concerning the role of VDAC expression regulation in neuronal cell survival in the brain and the significance of the mechanism to neurodegenerative disease including HD [108]. Accordingly, our preliminary results suggest interaction of human VDAC isoforms with both Htt and mHtt (unpublished results).

The issue implicates answering to the following three basic questions: (1) does the presence of mHtt result in changes of VDAC channel activity?; (2) do the changes in VDAC activity result from direct interaction of mHtt with VDAC or from the channel modification caused in the presence of mHtt or from the elimination of Htt effect?; (3) do the changes in VDAC activity trigger mitochondria dysfunction postulated for HD pathogenesis? Explaining whether VDAC defect is a causative event in HD pathogenesis and whether VDAC impairment is caused by its direct or indirect interaction with mHtt, could possibly narrow down the drug targets to be more specific and effective in blocking or controlling cell death by enabling the recovery of mitochondrial function and structure. Thus, resolving the role of VDAC in HD pathogenesis may be important for development...
of new therapeutic strategies concerning the disease as well as other neurodegenerative diseases.

Acknowledgement

The work was supported by grant from the National Science Centre (Poland), namely NCN - 2011/01/B/NN3/00359 and the “KNOW RNA Research Centre in Poznań” (grant no. 01/KNOW2/2014).

References

1. Bonelli RM, Hofmann P (2007) A systematic review of the treatment studies in Huntington’s disease since 1990. Expert Opin Pharmacother 8: 141-153.
2. Gövert F, Schneider SA (2013) Huntington’s disease and Huntington’s disease-like syndromes: an overview. Curr Opin Neurol 26: 420-427.
3. Glajch KE, Sadri-Vakili G (2015) Epigenetic Mechanisms Involved in Huntington’s Disease. Mov Disord 30: 1539-1546.
4. Kumar A, Kumar Singh S, Kumar V, Kumar D, Agarwal S et al. (2015) Huntington’s disease: an update of therapeutic strategies Gene 556: 91-97.
5. de Mezer M, Wojciechowska M, Napierala M, Sobczak K, Krzyzoskiak WJ (2011) Mutant CAG repeats of Huntington transcript fold into hairpins, form nuclear foci and are targets for RNA interference. Nucleic Acids Res 39: 3852-3863.
6. Hersch SM, Rosas HD (2008) Neuroprotection for Huntington’s disease: ready, set, slow. Neurotherapeutics 5: 226-236.
7. Kauffman JS, Zinovyeva A, Yagi K, Makabe KW, Raff RA (2003) Neural expression of the Huntington’s disease gene as a chordate evolutionary novelty. J Exp Zool B Mol Dev Evol 297: 57-64.
8. Pandey M, Mohanakumar KP, Usha R (2010) Mitochondrial functional alterations in relation to pathophysiology of Huntington’s disease. J Bioenerg Biomembr 42: 217-226.
9. Bocharova N, Chave-Cox R, Sokolov S, Knorre D, Severin F (2009) Protein aggregation and neurodegeneration: clues from a yeast model of Huntington’s disease. Biochemistry (Mosc) 74: 231-234.
10. Li SH, Schilling G, Young WS 3rd, Li XJ, Margolis RL, et al. (1993) Huntington’s disease gene (IT15) is widely expressed in human and rat tissues. Neuron 11: 985-993.
11. Godin JD, Colombo K, Molina-Calavita M, Keryg G, Zala D, et al. (2010) Huntington is required for mitotic spindle orientation and mammalian neurogenesis. Neuron. 67:392-406.
12. Li SH, Li XJ (2004) Huntingtoning and its role in neuronal degeneration. Neuroscientist 10: 467-475.
13. Kaltenbach LS, Romero E, Becklin RR, Chettier R, Bell R, et al. (2007) Huntington interacting proteins are genetic modifiers of neurodegeneration. PLoS Genet 3: e82.
14. Sak GH Jr (2010) Mitochondrial matters in Huntington disease. J Bioenerg Biomembr 42: 189-191.
15. Labbadia J, Morimoto RI (2013) Huntington’s disease: underlying molecular mechanisms and emerging concepts. Trends Biochem Sci 38: 378-385.
16. Civicchino A, Kwon YT (2015) Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies. Exp Mol Med 47: se147.
17. Glajch KE, Sadri-Vakili G (2015) Epigenetic Mechanisms Involved in Huntington’s Disease Pathogenesis. J Huntington’s Dis 4: 1-15.
18. Turner C, Schapira AH (2010) Mitochondrial matters of the brain: the role in Huntington’s disease. J Bioenerg Biomembr 42: 193-198.
19. Yano H, Baranow SV, Baranova OV, Kim J, Pan Y, et al. (2014) Inhibition of mitochondrial protein import by mutant huntingtin. Nat Neurosci 17: 822-831.
20. Safi C, Zange J, Andrich J, Müller K, Lindenberg K, et al. (2005) Mitochondrial impairment in patients and asymptomatic mutation carriers of Huntington’s disease. Mov Disord 20: 674-9.
21. Browne SE (2008) Mitochondria and Huntington’s disease pathogenesis: insight from genetic and chemical models. Ann N Y Acad Sci 1147: 358-382.
22. Damiano M, Galvan L, Déglon N, Brouillet E (2010) Mitochondria in Huntington’s disease. Biochim Biophys Acta 1802: 52-61.
23. Karachitos A, Galgańska H, Kmita H (2010) The role of mitochondria in the pathogenesis of Huntington’s disease. Postepy Biochem 56: 174-181.
24. Gellerich FN, Giatzullina Z, Trumbeckaite S, Nguyen HP, Pallas T, et al. (2010) The regulation of OXPHOS by extramitochondrial calcium. Biochim Biophys Acta1797: 1018-1027.
25. Shirideh EB, Calkins MJ, Manczak M, Anekonda V, Dufour B, et al. (2012) Mutant huntingtin’s interaction with mitochondrial protein Drp1 impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in Huntington’s disease. Hum Mol Genet 21: 406-420.
26. Costa V, Scorrano I (2012) Shaping the role of mitochondria in the pathogenesis of Huntington’s disease. EMBO J 31: 1853-1864.
27. Chakraborty J, Rajauma U, Mohankumar KP (2014) A mitochondrial basis for Huntington’s disease: therapeutic prospects. Mol Cell Biochem 389: 277-291.
28. Guedes-Dias P, Pinho BR, Soares TR, de Proença J, Duchen MR et al. (2015) Mitochondrial dynamics and quality control in Huntington’s disease. Neurobiol Dis.
29. Rostovtseva TK, Bezrukov SM (2012) VDAC inhibition by tubulin and its physiological implications. Biochim Biophys Acta 1818: 1526-1535.
30. Colombini M (2004) VDAC: the channel at the interface between mitochondria and the cytosol. Mol Cell Biochem 256-257:107-115.
31. Lemasters JJ, Holmuhamedov E (2006) Voltage-dependent anion channel (VDAC) as mitochondrial governor—thinking outside the box. Biochim Biophys Acta 1762: 181-190.
32. Mannella CA, Kinnally KW (2008) Reflections on VDAC as a voltage-gated channel and a mitochondrial regulator. J Bioenerg Biomembr 40: 149-155.
33. Shoshan-Barmatz V, De Pinto V, Zweekstetter M, Raviv Z, Keinan N et al. (2010) VDAC, a multi-functional mitochondrial protein regulating cell life and death. Mol Aspects Med 31: 227-285.
34. Galgańska H, Budzińska M, Wojtkowska M, Kmita H (2008) Redox regulation of protein expression in Saccharomyces cerevisiae mitochondria: possible role of VDAC. Arch Biochem Biophys 479: 39-45.
35. Galgańska H, Karachitos A, Baranek M, Budzińska M, Jordan J et al. (2010) Viability of Saccharomyces cerevisiae cells following exposure to H2O2 and protective effect of minocycline depend on the presence of VDAC. Eur J Pharmacol. 643: 42-47.
36. Galgańska H, Antoniewicz M, Budzińska M, Galgański L, Kmita H (2010) VDAC contributes to mRNA levels in Saccharomyces cerevisiae cells by the intracellular reduction/oxygenation state dependent and independent mechanisms. J Bioenerg Biomembr 42: 483-9.
37. Messina A, Reina S, Guarino F, De Pinto V (2012) VDAC isoforms in mammals. Biochim Biophys Acta 1818: 1466-1476.
38. Ferrer I (2009) Altered mitochondria, energy metabolism, voltage-dependent anion channel, and lipid rafts converge to exhaust neurons in Alzheimer’s disease. J Bioenerg Biomembr 41: 425-31.
39. Ramirez CM, Gonzalez M, Diaz M, Alonso R, Ferrer I, et al. (2009) VDAC and β-Ralphinteraction in caveolae from human cortex is altered in Alzheimer’s disease. Mol Cell Neurosci 42: 172-183.
43. Reddy PH (2013) Is the mitochondrial outer membrane protein VDAC1 therapeutic target for Alzheimer’s disease? Biochim Biophys Acta 1832:67-75.

44. Yoo BC, Fountoulakis M, Cairns N, Lubec G (2001) Changes of voltage-dependent anion-selective channel proteins VDAC1 and VDAC2 brain levels in patients with Alzheimer’s disease and Down syndrome. Electrophoresis 22:172-179.

45. Jiang W, Du B, Chen Z, Ma L, Wang S, et al. (2007) Preliminary explorations of the role of mitochondrial channels in refractory epilepsy: some findings from comparative proteomics. J Neurosci Res 85: 3160-3170.

46. Mostert JP, Koch MW, Heerings M, Heersena DJ, De Keyser J (2008) Therapeutic potential of fluoxetine in neurological disorders. CNS Neurosci Ther 14: 153-164.

47. Fukuda K, Zhang F, Vien A, Cashman NR, Zhu H (2004) Mitochondrial proteomic analysis of a cell line model of familial amyotrophic lateral sclerosis. Mol Cell Proteomics 3:1211-1223.

48. Israelson A, Arbel N, Da Cruz S, Ilieva H, Yamanaka K et al. (2010) Misfolded mutant SOD1 directly inhibits VDAC1 conductance in a mouse model of inherited ALS. Neuron 67: 575-587.

49. Brahim-Horn MC, Mazure NM (2014) Hypoxic VDAC1: a potential mitochondrial marker for cancer therapy. Adv Exp Med Biol 772: 101-110.

50. Blachly-Dynow M, Forte M (2001) VDAC channels. JUBMB Life. 52: 113-118.

51. McComis KS, Baines CP (2012) The role of VDAC in cell death: Friend or foe? Biochim Biophys Acta 1818: 1444-1450.

52. Raghavan A, Sheiko T, Graham BH, Craigen WJ (2012) Voltage-dependent anion channels: Novel insights into isofrom function through genetic models. Biochim Biophys Acta 1818: 1477-1485.

53. Kerner J, Lee K, Tandler B, Hoppel CL (2012) VDAC proteomics: Post-translation modifications. Biochim Biophys Acta 1818: 1520-1525.

54. Tewari SG, Zhou Y, Otto BJ, Dash RK, Kwok WM et al. (2015) Markov chain Monte Carlo based analysis of post-translationally modified VDAC gating kinetics. Front Physiol 5: 513.

55. Karachitos A, Galganska H, Ilieva H, Yamanaka K et al. (2010) Cu,Zn-superoxide dismutase is necessary for proper function of VDAC in Saccharomyces cerevisiae cells. FEBS Lett 583: 449-455.

56. Wawryn J, Swiecicki A, Bartosz G, Blinski T (2002) Effect of superoxide dismutase deficiency on the life span of the yeast Saccharomyces cerevisiae. An oxygen-independent role of Cu,Zn-superoxide dismutase. Biochim Biophys Acta 1570: 199-202.

57. O’Brien KM, Dirmeier R, Engle M, Poyton RO (2004) Mitochondrial proteomic analysis of a cell line model of familial amyotrophic lateral sclerosis. Mol Cell Proteomics 3:1211-1223.

58. Perluigi M, Poon HF, Maragos W, Mariani W, Klein JB et al. (2005) Proteomic analysis of protein expression and oxidative modification in r6/2 transgenic mice: a model of Huntington disease. Mol Cell Proteomics 4:1849-1861.

59. Ferrer I (2009) Altered mitochondria, energy metabolism, voltage-dependent anion channel, and lipid rafts converge to exhaust neurons in Alzheimer’s disease. J Bioenerg Biomembr 41:425-431.

60. Okazaki M, Kurabayashi K, Asanuma M, Saito Y, Dodo K et al. (2015) VDAC3 gating is activated by suppression of disulfide-bond formation between the N-terminal region and the bottom of the pore. Biochim Biophys Acta 1848: 3188-3196.

61. Schein SJ, Colombini M, Finkelstein A (1976) Reconstitution in planar lipid bilayers of a voltage-dependent anion-selective channel obtained from paramecium mitochondria. J Membr Biol 30: 99-120.

62. Benz R (1994) Permeation of hydrophilic solutes through mitochondrial outer membranes: review on mitochondrial porins. Biochim Biophys Acta 1197: 167-196.

63. Ziai M, Forte M, Blachly-Dynow M, Colombini M (1994) NADH regulates the gating of VDAC, the mitochondrial outer membrane channel. J Biol Chem 269:1614-1616.

64. Rostovtseva TK, Sheldon KL, Hassanzadeh E, Monge C, Saks V et al. (2008) Tubulin binding blocks mitochondrial voltage-dependent anion channel and regulates respiration. Proc Natl Acad Sci U S A 105: 18746-18751.

65. Rostovtseva TK, Bezkrukov SM (2012) VDAC inhibition by tubulin and its physiological implications. Biochim Biophys Acta 1818: 1526-1535.

66. Rostovtseva TK, Antonsson B, Suzuki M, Youle RJ, Colombini M et al. (2004) Bid, but not Bax, regulates VDAC channels. J Biol Chem 279: 13575-13583.

67. Vander Heiden MG, Chandel NS, Li XX, Schumacker PT, Colombini M et al. (2000) Outer mitochondrial membrane permeability can regulate coupled respiration and cell survival. Proc Natl Acad Sci U S A 97: 4666-4671.

68. Rostovtseva TK, Gurney PA, Protchenko O, Hoogerheide DP, Yap TL et al. (2015) α-Synuclein Shows High Affinity Interaction with Voltage-dependent Anion Channel, Suggesting Mechanisms of Mitochondrial Regulation and Toxicity in Parkinson Disease. J Biol Chem 290: 18467-77.

69. Veenman L, Sandalov Y, Gavish M (2008) VDAC activation by the 18 kDa translocator protein (TSPO), implications for apoptosis. J Bioenerg Biomembr 40: 199-205.

70. Veenman L, Gavish M (2012) The role of 18 kDa mitochondrial translocator protein (TSPO) in programmed cell death, and effects of steroids on TSPO expression. Curr Mol Med 12: 398-412.

71. Rostovtseva TK, Bezkrukov SM (2008) VDAC regulation: role of cytosolic proteins and mitochondrial lipids. J Bioenerg Biomembr 40: 163-170.

72. Karachitos A, Budzińska M, Stobienna O (2003) Modulation of the voltage-dependent anion-selective channel by cytoplasmic proteins from wild type and the channel depleted cells of Saccharomyces cerevisiae. Acta Biochim Pol 50: 415-424.

73. Shoshan-Barmatz V, Ben-Hal D (2012) VDAC, a multi-functional mitochondrial protein as a pharmacological target. Mitochondrion 12: 24-34.

74. Schwarzer C, Barnikol-Watanabe S, Thinesse FP, Hilschmann N (2002) Voltage-dependent anion-selective channel (VDAC) interacts with the dynnein light chain Tic1ex1 and the heat-shock protein PBP74. Int J Biochem Cell Biol 34:1059-1070.

75. Park J, Kim Y, Choi S, Koh H, Lee SH, et al. (2010) Drosophila Porin/VDAC affects mitochondrial morphology. PLoS One 5: e13151.

76. Peitzko PM, Dejean LM, Kinnally KW (2012) The therapeutic potential of mitochondrial channels in cancer, ischemia-reperfusion injury, and neurodegeneration. Mitochondrion 12: 14-23.

77. Karachitos A, Garcia Del Pozo JS, de Groot PW, Kmita H, Jordan J (2013) Minocycline mediated mitochondrial cytoprotection: premises for therapy of cerebrovascular and neurodegenerative diseases. Curr Drug Targets 14: 47-55.

78. Ralph SJ, Low P, Dong L, Lawen A, Neuzil J (2006) Mitocams: mitochondrial targeted anti-cancer drugs as improved therapies and related patent documents. Recent Pat Anticancer Drug Discov 1: 327-346.

79. Rohlena J, Dong LF, Ralph SJ, Neuzil J (2011) Anticancer drugs targeting the mitochondrial electron transport chain. Antioxid Redox Signal 15: 2951-2974.

80. Yagoda N, von Rechenberg M, Zaganjor E, Bauer AJ, Yang WS, et al. (2004) Bid, but not Bax, regulates VDAC channels. J Biol Chem 279: 51817-51827.

81. Simamura E, Shimada H, Ishigaki Y, Hatta T, Higashi N et al. (2008) Krox24-34. Thinnes FP (2009) Human type-1 VDAC, a cisplatin target involved in drug ef ﬁ ciency. PLoS One 5: e13151.

82. Vander Heiden MG, Chandel NS, Li XX, Schumacker PT, Colombini M et al. (2000) Outer mitochondrial membrane permeability can regulate coupled respiration and cell survival. Proc Natl Acad Sci U S A 97: 4666-4671.
83. Bauer Al, Giescher S, Lemberg KM, McDermott AE, Stockwell BR (2011) Functional model of metabolite gating by human voltage-dependent anion channel 2. Biochemistry 50: 3408-3410.

84. Krasnov GS, Dmitriev AA, Lakanina VA, Kirpiy AA, Kudryavtseva AV (2013) Targeting VDAC-bound hexokinase II: a promising approach for concomitant anti-cancer therapy. Expert Opin Ther Targets 17: 1221-1233.

85. Zheng Y, Shi Y, Tan C, Jiang C, Jin H, et al. (2004) Essential role of the voltage-dependent anion channel (VDAC) in mitochondrial permeability transition pore opening and cytochrome c release induced by arsenic trioxide. Oncogene 23: 1239-1247.

86. Lai JC, Tan W, Benimetskaya L, Miller P, Colombini M et al. (2006) A novel plant-derived metabolite lowers energy metabolism in tumor cells by targeting the outer mitochondrial membrane. Mitochondrion 7: 234-240.

87. Galluzzi L, Vitale I, Kepp O, Séror C, Hangan E, et al. (2008) Methods to dissect mitochondrial membrane permeabilization in the course of apoptosis. Methods Enzymol 442: 355-374.

88. Haridas V, Li X, Mizumachi T, Higuchi M, Lemeshko VV et al. (2007) Aviscins, a novel plant-derived metabolite lowers energy metabolism in tumor cells by targeting the outer mitochondrial membrane. Mitochondrion 7: 234-240.

89. Palmieri B, Iannitti T, Capone S, Flescher E (2011) A preliminary study of the local treatment of preneoplastic and malignant skin lesions using methyl jasmonate. Eur Rev Med Pharmacol Sci 15: 333-336.

90. Naranmandura H, Chen X, Tanaka M, Wang WW, Rehman K et al. (2012) Release of apoptotic cytochrome C from mitochondria by dimethylarsinous acid occurs through interaction with voltage-dependent anion channel in vitro. Toxicol Sci 128: 137-146.

91. Tang W, Loke YH, Stein CA, Miller P et al. (2007) Phosphorothioate oligonucleotides block the VDAC channel. Biophys J 93: 1184-1191.

92. Tan W (2012) VDAC blockage by phosphorothioate oligonucleotides and its implication in apoptosis. Biochim Biophys Acta 1818: 1555-1561.

93. Azarashvili T, Krestinina O, Baburina Y, Odinokova I, Grachev D, et al. Combined effect of G3139 and TSPO ligands on Ca(2+)-induced permeability transition in rat brain mitochondria. Arch Biochem Biophys 587: 70-77.

94. Lauterbach EC, Shilkhet SD, Victoroff J, Coburn KL, Mendez MF (2010) Psychopharmacological neuroprotection in neurodegenerative disease: heuristic clinical applications. J Neuropsychiatry Clin Neurosci 22: 130-154.

95. Youdim MB, Weinstock M (2001) Molecular basis of neuroprotective activities of rasagiline and the anti-Alzheimer drug TV3326 [(N-propargyl-(3R)-aminomindan-5-YL)-ethyl methyl carbamate]. Cell Mol Neurobiol 21: 555-573.

96. Youdim MB (2003) Rasagiline: an anti-Parkinson drug with neuroprotective activity. Expert Rev Neurother. 3: 737-749.

97. Plane JM, Shen Y, Pleasure DE, Deng W (2010) Prospects for minocycline neuroprotection. Arch Neurol 67: 1442-1448.

98. Karachitos A, García Del Pozo JS, de Groot PW, Kmita H, Jordan J (2012) Minocycline mediated mitochondrial cytoprotection: premises for therapy of cerebrovascular and neurodegenerative diseases. Curr Drug Targets 14: 47-55.

99. Bonelli RM, Hödl AK, Hofmann P, Kapfhammer HP (2004) Neuroprotection in Huntington's disease: a 2-year study on minocycline. Int Clin Psychopharmacol 19: 337-342.

100. Yuan S, Fu Y, Wang X, Shi H, Huang Y, et al. (2008) Voltage-dependent anion channel 1 is involved in endostatin-induced endothelial cell apoptosis. FASEB J 22: 2809-2820.

101. Sharaf el dein O, Gallerne C, Brenner C, Lemaire C (2012) Increased expression of VDAC1 sensitizes carcinoma cells to apoptosis induced by DNA cross-linking agents. Biochem Pharmacol 83: 1172-1182.

102. Ouyang L, Shi Z, Zhao S, Wang FT, Zhou TT et al. (2012) Programmed cell death pathways in cancer: a review of apoptosis, autophagy and programmed necrosis. Cell Prolif 45: 487-498.

103. Chabaane W, User SD, El-Gazzah M, Jaksik R, Sajjadi E et al. (2013) Autophagy, apoptosis, mitoposis and necrosis: interdependence between those pathways and effects on cancer. Arch Immunol Ther (Warsz) 61: 43-58.

104. Li WW, Li J, Yao JK (2012) Microautophagy: lesser-known self-eating. Cell Mol Life Sci 69: 1125-1136.

105. Xiong Y, Ding H, Xu M, Gao J (2009) Protective effects of asiatic acid on rotenone- or H2O2-induced injury in SH-SY5Y cells. Neurochem Res 34: 746-754.

106. Roshan R, Shridhar S, Sarangdhar MA, Banik A, Chawla M, et al. (2014) Brain-specific knockdown of miR-29 results in neuronal cell death and ataxia in mice. RNA. 20: 1287-1297.

107. Garcia-Martinez EM, Sanz-Blasco S, Karachitos A, Bandez MJ, Fernandez-Gomez FJ et al. (2010) Mitochondria and calcium flux as targets of neuroprotection caused by minocycline in cerebellar granule cells. Biochem Pharmacol. 79: 239-250.

108. Chaudhry IB, Hallak J, Husain N, Minhias F, Sother J et al. (2012) Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J Psychopharmacol 26: 1185-1193.

109. Miyaoka T, Wake R, Furuya M, Liaury K, Ieda M et al. (2012) Minocycline as adjunctive therapy for patients with unipolar psychotic depression: an open-label study. Prog Neuropsychopharmacol Biol Psychiatry 37: 222-226.

110. Casha S, Zigun D, McGowan MD, Bains I, Yong VW et al. (2012) Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. Brain 135: 1224-1236.