Biochimica et Biophysica Acta 1797 (2010) 1276–1280

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Review

Communication between mitochondria and nucleus: Putative role for VDAC in reduction/oxidation mechanism

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ARTICLE INFO

Article history:
Received 13 November 2009
Received in revised form 1 February 2010
Accepted 1 February 2010
Available online 6 February 2010

Keywords:
VDAC
Superoxide anion
Cytosol redox state
Expression of mitochondrial proteins

ABSTRACT

Voltage dependent anion channel (VDAC) was identified in 1976 and since that time has been extensively studied. It is well known that VDAC transports metabolites across the outer mitochondrial membrane. The simple transport function is indispensable for proper mitochondria functions and, consequently for cell activity, and makes VDAC crucial for a range of cellular processes including ATP rationing, Ca^{2+} homeostasis and apoptosis execution. Here, we review recent data obtained for *Saccharomyces cerevisiae* cells used as a model system concerning the putative role of VDAC in communication between mitochondria and the nucleus. The *S. cerevisiae* VDAC isoform known as VDAC1 (termed here YVDAC) mediates the cytosol reduction/oxidation (redox) state that contributes to regulation of expression and activity of cellular proteins including proteins that participate in protein import into mitochondria and antioxidant enzymes. Simultaneously, copper-and-zinc-containing superoxide dismutase (CuZnSOD) plays an important role in controlling YVDAC activity and expression levels. Thus, it is proposed that VDAC constitutes an important component of a regulatory mechanism based on the cytosol redox state.

1. Introduction

Tight coordination between the nucleus and mitochondria is required for proper mitochondrial functioning and includes both anterograde (nucleus to mitochondria) and retrograde (mitochondria to nucleus) signals [1–5]. The anterograde mechanisms coordinate gene expression in mitochondria in response to endogenous and environmental signals that are perceived by the nucleus, whereas retrograde mechanisms transmit signals that originate in mitochondria to regulate nuclear gene expression, which can then modify anterograde control. Signals relevant to the retrograde mechanisms can involve reactive oxygen species (ROS) generated and released by mitochondria because the ROS release contributes to intracellular reduction/oxidation (redox) homeostasis and to the regulation of signaling cascades [6–10]. However, when the release evades or overcomes cell defences, ROS can damage a wide range of macromolecules in the cell, including nucleic acids, proteins and lipids, eventually leading to cell dysfunction and death [8,11–13].

The ROS generated and released by mitochondria are mainly by-products of cellular energy transformation performed by the mitochondrial respiratory chain. The best known ROS originating from mitochondria are superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2), a product of $O_2^{\bullet -}$ dismutation. A fundamental defence against $O_2^{\bullet -}$ is superoxide dismutase (SOD) present in eukaryotic cells as a manganese-containing enzyme (MnSOD or SOD2) located in the mitochondrial matrix and as a copper-and-zinc-containing enzyme (CuZnSOD or SOD1) located in different cell types in various compartments including cytosol and the intermembrane space of mitochondria [8,14–18]. Both MnSOD and CuZnSOD catalyze dismutation of $O_2^{\bullet -}$ to molecular oxygen and H_2O_2 that can be converted to water by other antioxidant enzymes or to the hydroxyl radical in the presence of some transition metals [19]. However, it is also known that CuZnSOD is able to catalyze nitration of protein tyrosines [20] and has peroxidase [21] and thiol oxidase [22] activities. Thus, MnSOD and CuZnSOD display both protective and pro-oxidant properties, depending on existing conditions [23–25]. Consequently, excessive or deficient activity of MnSOD and CuZnSOD may be involved in etiology of some diseases.

It has been shown that H_2O_2 diffuses rapidly through membranes [26] and its release from mitochondria to the cytosol reflects the balance between its production and consumption reactions [6]. However, $O_2^{\bullet -}$ is generally membrane-impermeable [27,28] and exits mitochondria via channels of the outer mitochondrial membrane, namely the channel of the TOM complex [29] and VDAC [6]. The TOM complex (translocase of the outer mitochondrial membrane) is a

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doi:10.1016/j.bbabio.2010.02.004

part of the mitochondrial protein import machinery (for reviews see, for example, [30–33]). VDAC (voltage dependent anion channel), the main channel of the outer mitochondrial membrane, is also known as mitochondrial porin (for reviews see, for example, [34–39]). Physiologically, VDAC functions as a major channel allowing passage of metabolites between the intermembrane space of mitochondria and the cytosol. The channel may be present as isoforms encoded by separated genes, displaying different channel-forming activities and probably playing different roles. It has been shown that VDAC plays a crucial role in ATP rationing, Ca^{2+} homeostasis, and apoptosis execution. This review will consider VDAC involvement in the determination of the intracellular redox states important for the redox regulation of cellular protein expression and activity. The discussed data refer to *Saccharomyces cerevisiae* cells used as a model system. The involvement of VDAC in the regulatory process is consistent with data pointing at VDAC as an important element of intracellular signaling [3,40].

2. The yeast *S. cerevisiae* as a model system to study the involvement of VDAC in redox mechanisms

The yeast *S. cerevisiae* is a convenient model to investigate the functional relationship between VDAC, the redox states of cell compartments (e.g., mitochondria and cytosol) and expression levels and/or activity of cellular proteins. Firstly, *S. cerevisiae* mitochondria express two VDAC isoforms, of which only one has been proved to form a channel [41]. The VDAC isoform encoded by the *POR1* gene is called VDAC1 (or porin 1) and its properties are highly conserved in other species. The second VDAC protein of still unknown function, encoded by the *POR2* gene, is called VDAC2 (or porin 2) and does not display a channel-forming activity. To emphasize the difference between the mammalian and yeast VDAC2 the term YVDAC2 is used here for the yeast protein. Since only VDAC1 forms channels in *S. cerevisiae* mitochondria, the protein is termed here YVDAC. The presence of only one channel-forming VDAC isoform in *S. cerevisiae* mitochondria simplifies studies of the channel. Secondly, depletion of YVDAC or YVDAC2 (Δ*por1* and Δ*por2* mutants, respectively) distinctly affects the metabolite passage across the outer membrane of *S. cerevisiae* mitochondria [42,43] as well as expression levels of some of the membrane proteins and their encoding mRNAs [44,45]. Thirdly, wild type and a given VDAC isoform mutant of *S. cerevisiae* display differences in the cytosol and mitochondrial redox states. The redox states coincide with the level of $O_2^{\bullet-}$ release from mitochondria and can be imitated by modification of growth conditions of the cells by addition of an oxidant or antioxidant to the growth medium, depending on the strain studied [10,29,46]. Therefore *S. cerevisiae* is a convenient model to study the activity and/or expression levels of cellular proteins under conditions of differentiated redox states of the cytosol and mitochondria.

3. Proper function of VDAC requires the presence of CuZnSOD

As mentioned in the Introduction, superoxide dismutases (SOD) are fundamental components of the defence system against $O_2^{\bullet-}$ generated mainly by mitochondrial respiration. The defence, among other effects, protects proteins against oxidation damage. Interestingly, it has been reported for *S. cerevisiae* that one of the protected proteins is YVDAC that is highly sensitive to oxidative damage [18,47]. Moreover, it is known that in *S. cerevisiae* cells CuZnSOD accounts for 90–95% of the total SOD activity and, consequently, a phenotype of SOD1-deleted mutant (Δ*sod1*) is much more pronounced than that of SOD2-deleted one (Δ*sod2*) [18,48]. Accordingly, it has been reported that CuZnSOD plays an important role in controlling YVDAC channel activity and expression levels [49]. As determined by a reconstituted system, lack of proper CuZnSOD activity in *S. cerevisiae* cells promotes YVDAC closing and decreases the voltage dependence of the channel. The data points at an impairment of YVDAC gating mechanism. It has similarly been shown for mouse VDAC2 isoform that mutation neutralizing the voltage sensor results in a channel that lacks voltage gating and displays lower conductance [50]. VDAC gating is currently regarded as the major mechanism of the outer mitochondrial membrane permeability control [51]. Thus, in the absence of a functional CuZnSOD the control might be severely affected. This in turn, probably imposes distinct effects on metabolite exchange between mitochondria and the cytosol.

It is also known that CuZnSOD plays an important role in maintaining a normal replicative life span of *S. cerevisiae* [48]. Therefore, it could be hypothesized that the substantial shortening of the replicative life span observed for Δ*sod1* mutants may result from disturbed functioning of mitochondria caused by improper permeability of the outer membrane due to impairment of YVDAC function. Alternatively, the lower conductance states of YVDAC could protect the mutant cells against $O_2^{\bullet-}$ release from the intermembrane space of mitochondria to the cytosol via VDAC. Thus, VDAC might serve as a sensor for mitochondrial $O_2^{\bullet-}$ levels. It can be speculated that the sensing mechanism probably consists in a VDAC protein modification by the $O_2^{\bullet-}$ not dismutated by CuZnSOD. The possibility of the modification would increase in the presence of higher $O_2^{\bullet-}$ release from mitochondria, which in turn would increase the likelihood of VDAC gating impairment resulting in lower conductance states of VDAC. Consequently, smaller amounts of $O_2^{\bullet-}$ would be released from the intermembrane space of mitochondria to the cytosol via VDAC. This effect could be protective in cases of excessive $O_2^{\bullet-}$ release but could also perturb mitochondria-dependent redox signaling [52]. On the other hand the substantial shortening of the replicative life span reported for *S. cerevisiae* cells depleted of CuZnSOD may result from reduction in YVDAC levels in mitochondria [49]. A moderate decrease in VDAC levels is also observed for mitochondria of mice deficient in CuZnSOD [53]. VDAC deficiency has been reported to result in mitochondriopathy [54,55] that in turn makes cells susceptible to stress and aging [56]. It cannot be excluded that the reduction in VDAC levels in mitochondria may result from oxidative damage caused by the absence of a functional CuZnSOD and subsequent degradation [53]. However, it is also possible that the reduction is caused by an impairment of YVDAC import machinery because it has been shown for *S. cerevisiae* that depletion of CuZnSOD also affects levels of the outer mitochondrial membrane proteins crucial for VDAC import into mitochondria [49], namely the TOM complex and the TOB/SAM complex (for reviews see, for example, [30–33]). Interestingly, the expression levels of subunits of TOM and TOB/SAM complexes are influenced by YVDAC [10,46]. Therefore the changed functioning of VDAC in the absence of CuZnSOD may affect the expression levels of the components of the VDAC import machinery that in turn influences VDAC levels in mitochondria. Interestingly, it has been reported recently that VDAC level is important for a mechanism playing a causal role in oxidative stress-induced apoptosis [57].

4. VDAC mediates the redox state of the cytosol and mitochondria

The cytosol and mitochondria redox states in *S. cerevisiae* cells change during their growth [10,46,58]. The latest data indicates that the redox states are also distinctly influenced by the deletion of a given VDAC isoform. It has been reported that exponentially and stationary growing *S. cerevisiae* cells depleted of YVDAC or YVDAC2 (Δ*por1* and Δ*por2*, respectively) display differences in values of the cytosol and mitochondria redox states when compared to the isogenic wild type and to each other [10,46]. Accordingly, the activities of the cytosol (CuZnSOD, catalase) and mitochondrial (MnSOD, glutathione peroxidase and glutathione reductase) antioxidant enzymes are also influenced by the absence of either yeast VDAC isoform and coincide with the observed changes of the redox states [46]. In general, the redox state shift towards oxidation results in an increase in the enzyme activities, whereas the redox state change towards reduction

decreases these activities. Intriguingly, the expression levels of MnSOD and CuZnSOD are also influenced by the deletion of a given yeast VDAC isoform [10,46]. Since antioxidant enzymes protect cells against dangerous changes of redox states contributing simultaneously to the existing redox states and the expression levels and activities of the cytosol and mitochondrial antioxidant enzymes are influenced by the absence of either yeast VDAC isoform, it could be concluded that VDAC influences the redox states of the cytosol and mitochondria. Moreover, at least partially, the effect of VDAC in *S. cerevisiae* cells does not depend on its channel activity.

Regarding differences concerning the cytosol and mitochondria redox states observed for wild type, Δ*por1* and Δ*por2* cells, it is suggested that the redox state of the cytosol is mainly mediated by YVDAC, although YVDAC2 has a quantitative effect as well, whereas the redox state of mitochondria depends on the presence of both YVDAC and YVDAC2 [46]. Interestingly, the direction of the redox state shift during cell growth (i.e., towards oxidation or reduction) is the same in mitochondria and the cytosol only in the presence of YVDAC2. It is therefore proposed that YVDAC2 is also necessary for the coordination of the redox state levels between mitochondria and the cytosol. These observations implicate two kinds of mechanisms of VDAC effects on the redox state in *S. cerevisiae* cells: a non-channel and a channel-based one [46]. Both are probably important for communication between mitochondria and the nucleus [3]. However, it should be remembered that the cytosol redox state may be also influenced by other cell processes and organelles. For example, it is well know that the endoplasmic reticulum participates in intracellular redox homeostasis [59]. Consistently, VDAC has been also detected in the endoplasmic reticulum membranes [60], however, its role in the redox state controlling is not known. It is also still unclear how YVDAC and YVDAC2 contribute to the redox states of the cytosol and mitochondria. It can be speculated that they transport metabolites that participate in the determination of the redox states. Interestingly, the differences in the cytosol redox states observed for wild type, Δ*por1* and Δ*por2* cells coincide with the differences in the levels of $O_2^{\bullet -}$ release from their mitochondria [10,29]. The levels of the release may be modified by the activity of CuZnSOD located in the mitochondrial intermembrane space, as it has been shown that activity of the enzyme depends on the presence of a given yeast VDAC isoform [10].

5. The cytosol redox state is crucial for the expression levels of mitochondrial proteins

The intracellular redox states denote redox states of cell compartments, e.g., the cytosol and mitochondria. Interestingly, it has been reported that *S. cerevisiae* cells depleted of YVDAC or YVDAC2 (Δ*por1* and Δ*por2*, respectively) display differences in levels of $O_2^{\bullet -}$ release from mitochondria that coincide with differences in the cytosol redox state [10,29]. Simultaneously, the cells differ in the expression levels of subunits of the TOM and TOB/SAM complexes, i.e., Tom70, Tom40 and Tob55/Sam50 [10,44–46]. Since the intracellular redox states are known to affect expression, stability, localization, accessibility, interactions and activity of proteins [3,4,7], it has been proposed that the cytosol redox state modulates the expression levels of subunits of the TOM and TOB/SAM complexes in *S. cerevisiae* mitochondria [46]. To verify this hypothesis, the relations between the calculated cytosol and mitochondria redox states and the expression levels of Tom70, Tom40 and Tob55/Sam50 were analyzed for wild type, Δ*por1* and Δ*por2* mitochondria isolated from cells in the exponential, stationary and modified exponential growth phases [46]. The latter denotes an exponential growth phase modified toward the stationary growth phase with regard to the cytosol and mitochondria redox states. For the modification, an oxidant or an antioxidant were added to a given cell culture at the early exponential growth phase and cells were grown until standard exponential phase [46]. The applied experimental strategy is summarized in Fig. 1. It has been

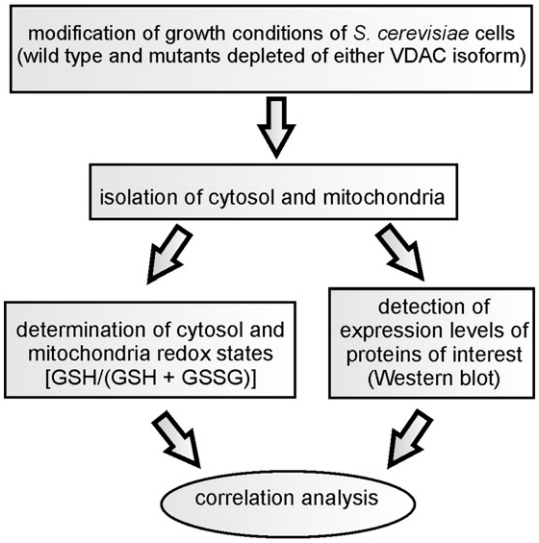

Fig. 1. Strategy applied in experiments concerning role of VDAC in reduction/oxidation mechanism.

shown that modifications of the cytosol redox state, but not the mitochondria one, towards a given status trigger the expected changes of the expression levels of Tom70, Tom40 and Tob55/Sam50. It means that the modification of the exponential growth phase toward stationary growth phase with regard to the cytosol redox state results in the expression levels of the studied proteins in mitochondria typical for the stationary growth phase. The expression of the studied proteins increases when the cytosol redox state becomes more oxidized although the oxidation may occur in different growth phases, depending on the *S. cerevisiae* strain studied. Moreover, in the case of Tom proteins and Tob55/Sam50, effects of inhibitors of transcription and translation support the important role of the cytosol redox state in the regulation of expression of these proteins (unpublished results). Interestingly, MnSOD and CuZnSOD in cytosol seem to share the mechanism of expression regulation with Tom70, Tom40 and Tob55 [46]. Thus, the mechanism is not confined to subunits of the protein import machinery of the outer mitochondrial membrane. Therefore, it could be suggested that the cytosol redox state may influence the activity of cytoplasmic regulatory proteins and/or nuclear transcription factors responsible for the expression levels of mitochondrial proteins encoded by nuclear genes.

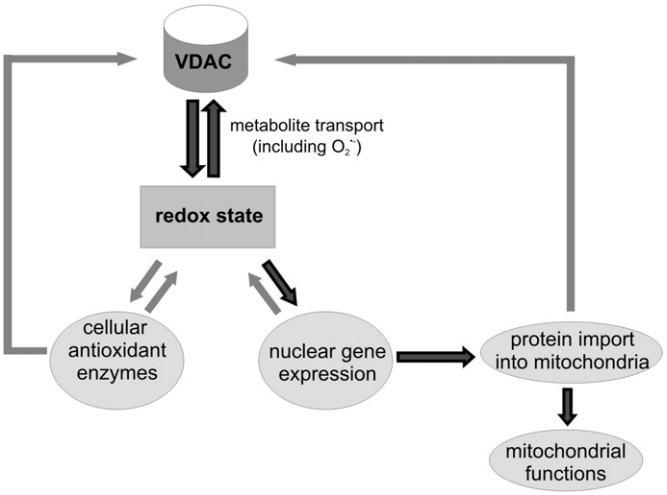

Fig. 2. Schematic diagram of VDAC mediated reduction/oxidation mechanism involved in regulation of expression and activity of mitochondrial proteins.

Thus, the cytosol redox state participates in communication between mitochondria and the nucleus.

6. Implications for the redox mechanism mediated by VDAC

The changes of the expression levels of mitochondrial proteins triggered by the redox mechanism mediated mainly by YVDAC are crucial for mitochondrial functions. For example, changes of the expression levels of the TOM complex subunits, i.e., Tom proteins, may contribute to supplementary functions of the complex. Accordingly, it has been reported that the expression level of Tom40, a crucial subunit of the TOM complex, correlates with the complex involvement in metabolite transport across the outer membrane as well as with levels of $O_2^{\bullet-}$ release from *S. cerevisiae* mitochondria [29,44,61]. In the case of *S. cerevisiae*, the TOM complex may serve as a supplementary pathway for metabolites across the outer membrane, even in the presence of YVDAC, although the role of the TOM complex increases when YVDAC is depleted. Similarly, the involvement of the TOM complex in $O_2^{\bullet-}$ release from *S. cerevisiae* mitochondria is enhanced in the absence of YVDAC but also occurs in the presence of the isoform, particularly under conditions that trigger high levels of $O_2^{\bullet-}$ release. On the other hand, the cytosol redox state mediated mainly by YVDAC is important for the regulation of levels of mRNA encoding not only Tom proteins but also other proteins that participate in protein import into mitochondria, as well as proteins that are involved in mitochondria distribution and morphology, the mitochondria/nucleus communication and antioxidant activity (unpublished results). Simultaneously, CuZnSOD, a fundamental defence against $O_2^{\bullet-}$ contributes to YVDAC proper activity and expression levels [49]. The putative role of VDAC in redox mechanism involved in regulation of expression and activity of mitochondrial proteins is summarized in Fig. 2. In conclusion, taking into account the data obtained for the model system of *S. cerevisiae* cells, it is proposed that VDAC is an important element of a protein network that control functions of mitochondria by contributing to the cytosol redox state and/or by sensing the redox state. This is in agreement with the growing number of data showing that VDAC is a dynamic regulator, or even governor, of mitochondrial functions [39,42,51]. Consistently, it has been shown that VDAC can be regarded as a candidate for effective pharmacological treatment, for example in anticancer therapy [62,63].

References

[1] J.F. Allen, The function of genomes in bioenergetic organelles, Philos. Trans. R. Soc. Lond. B Biol. Sci. 358 (2003) 19–37.
[2] R.A. Butow, N.G. Avadhani, Mitochondrial signaling: the retrograde response, Mol Cell. 14 (2004) 1–15.
[3] P. Pesaresi, A. Schneider, T. Kleine, D. Leister, Interorganellar communication, Curr. Opin. Plant Biol. 10 (2007) 600–606.
[4] J.D. Woodson, J. Chory, Coordination of gene expression between organellar and nuclear genomes, Nat. Rev. Genet. 9 (2008) 383–395.
[5] G. Cannino, C.M. Di Liegro, A.M. Rinaldi, Nuclear–mitochondrial interaction, Mitochondrion 7 (2007) 359–366.
[6] D. Han, F. Antunes, R. Canali, D. Rettori, E. Cadenas, Voltage-dependent anion channels control the release of the superoxide anion from mitochondria to cytosol, J. Biol. Chem. 278 (2003) 5557–5563.
[7] H. Liu, R. Colavitti, I.I. Rovira, T. Finkel, Redox-dependent transcriptional regulation, Circ. Res. 97 (2005) 967–974.
[8] P. Storz, Reactive oxygen species-mediated mitochondria-to-nucleus signaling: a key to aging and radical-caused diseases, Sci STKE (2006) re3.
[9] T. Finkel, Intracellular redox regulation by the family of small GTPases, Antioxid. Redox Signal. 8 (2006) 1857–1863.
[10] M. Budzinska, H. Galganska, M. Wojtkowska, O. Stobienia, H. Kmita, Effects of VDAC isoforms on CuZn-superoxide dismutase activity in the intermembrane space of *Saccharomyces cerevisiae* mitochondria, Biochem. Biophys. Res. Commun. 357 (2007) 1065–1070.
[11] M.R. Duchen, Roles of mitochondria in health and disease, Diabetes 53 (Suppl 1) (2004) S96–S102.
[12] M. Monsalve, S. Borniquel, I. Valle, S. Lamas, Mitochondrial dysfunction in human pathologies, Front Biosci. 12 (2007) 1131–1153.
[13] A.A. Fatokun, T.W. Stone, R.A. Smith, Oxidative stress in neurodegeneration and available means of protection, Front Biosci. 13 (2008) 3288–3311.
[14] J. St-Pierre, J.A. Buckingham, S.J. Roebuck, M.D. Brand, Topology of superoxide production from different sites in the mitochondrial electron transport chain, J. Biol. Chem. 277 (2002) 44784–44790.
[15] V.C. Culotta, M. Yang, T.V. O'Halloran, Activation of superoxide dismutases: putting the metal to the pedal, Biochim. Biophys. Acta 1763 (2006) 747–758.
[16] P. Jezek, L. Hlavatá, Mitochondria in homeostasis of reactive oxygen species in cell, tissues, and organism, Int. J. Biochem. Cell Biol. 37 (2005) 2478–2503.
[17] L.A. Sturtz, K. Diekert, L.T. Jensen, R. Lill, V.C. Culotta, A fraction of yeast Cu, Zn-superoxide dismutase and its metallochaperone, CCS, localize to the intermembrane space of mitochondria. A physiological role for SOD1 in guarding against mitochondrial oxidative damage, J. Biol. Chem. 276 (2001) 38084–38089.
[18] K.M. O'Brien, R. Dirmeier, M. Engle, R.O. Poyton, Mitochondrial protein oxidation in yeast mutants lacking manganese-(MnSOD) or copper- and zinc-containing superoxide dismutase (CuZnSOD): evidence that MnSOD and CuZnSOD have both unique and overlapping functions in protecting mitochondrial proteins from oxidative damage, J. Biol. Chem. 279 (2004) 51817–51827.
[19] S.J. Stohs, D. Bagchi, Oxidative mechanisms in the toxicity of metal ions, Free Radic. Biol. Med. 18 (1995) 321–336.
[20] J.S. Beckman, Oxidative damage and tyrosine nitration from peroxynitrite, Chem. Res. Toxicol. 5 (1996) 836–844.
[21] S.Z. Potter, J.S. Valentine, The perplexing role of copper-zinc superoxide dismutase in amyotrophic lateral sclerosis (Lou Gehrig's disease), J. Biol. Inorg. Chem. 8 (2003) 373–380.
[22] C.C. Winterbourn, A.V. Peskin, H.N. Parsons-Mair, Thiol oxidase activity of copper, zinc superoxide dismutase, J. Biol. Chem. 277 (2002) 1906–1911.
[23] R.M. Tamimi, S.E. Hankinson, D. Spiegelman, G.A. Colditz, D.J. Hunter, Manganese superoxide dismutase polymorphism, plasma antioxidants, cigarette smoking, and risk of breast cancer, Cancer Epidemiol. Biomarkers Prev. 13 (2004) 989–996.
[24] V. Lushchak, H. Semchyshyn, S. Mandryk, O. Lushchak, Possible role of superoxide dismutases in the yeast *Saccharomyces cerevisiae* under respiratory conditions, Arch. Biochem. Biophys. 441 (2005) 35–40.
[25] G. Goldsteins, V. Keksa-Goldsteine, T. Ahtoniemi, M. Jaronen, E. Arens, K. Akerman, P.H. Chan, J. Koistinaho, Deleterious role of superoxide dismutase in the mitochondrial intermembrane space, J. Biol. Chem. 283 (2008) 8446–8452.
[26] F. Antunes, E. Cadenas, Estimation of H_2O_2 gradients across biomembranes, FEBS Lett. 475 (2000) 121–126.
[27] R.A. Gus'kova, I.I. Ivanov, V.K. Kol'tover, V.V. Akhobadze, A.B. Rubin, Permeability of bilayer lipid membranes for superoxide ($O_2^{\cdot-}$) radicals, Biochim. Biophys. Acta 778 (1984) 579–585.
[28] D. Han, E. Williams, E. Cadenas, Mitochondrial respiratory chain-dependent generation of superoxide anion and its release into the intermembrane space, Biochem. J. 353 (2001) 411–416.
[29] M. Budzińska, H. Gałgańska, A. Karachitos, M. Wojtkowska, H. Kmita, The TOM complex is involved in the release of superoxide anion from mitochondria, J. Bioenerg. Biomembr. 41 (2009) 361–367.
[30] P. Dolezal, V. Likic, J. Tachezy, T. Lithgow, Evolution of the molecular machines for protein import into mitochondria, Science 313 (2006) 314–318.
[31] M. Bohnert, N. Pfanner, M. van der Laan, A dynamic machinery for import of mitochondrial precursor proteins, FEBS Lett. 581 (2007) 2802–2810.
[32] T. Becker, F.N. Vögtle, D. Stojanovski, C. Meisinger, Sorting and assembly of mitochondrial outer membrane proteins, Biochim. Biophys. Acta 1777 (2008) 557–563.
[33] D. Mokranjac, W. Neupert, Thirty years of protein translocation into mitochondria: unexpectedly complex and still puzzling, Biochim. Biophys. Acta 1793 (2009) 33–41.
[34] R. Benz, Permeation of hydrophilic solutes through mitochondrial outer membranes: review on mitochondrial porins, Biochim. Biophys. Acta 1197 (1994) 167–196.
[35] E. Blachly-Dyson, M. Forte, VDAC channels, IUBMB Life 52 (2001) 113–118.
[36] V. De Pinto, A. Messina, R. Accardi, R. Aiello, F. Guarino, M.F. Tomasello, M. Tommasino, G. Tasco, R. Casadio, R. Benz, F. De Giorgi, F. Ichas, M. Baker, A. Lawen, New functions of an old protein: the eukaryotic porin or voltage dependent anion selective channel (VDAC), Ital. J. Biochem. 52 (2003) 17–24.
[37] M. Colombini, VDAC: the channel at the interface between mitochondria and the cytosol, Mol. Cell. Biochem. 256–257 (2004) 107–115.
[38] V. Shoshan-Barmatz, N. Keinan, H. Zaid, Uncovering the role of VDAC in the regulation of cell life and death, J. Bioenerg. Biomembr. 40 (2008) 183–191.
[39] C.A. Mannella, K.W. Kinnally, Reflections on VDAC as a voltage-gated channel and a mitochondrial regulator, J. Bioenerg. Biomembr. 40 (2008) 149–155.
[40] J.J. Lemasters, E. Holmuhamedov, Voltage-dependent anion channel (VDAC) as mitochondrial governator—thinking outside the box, Biochim. Biophys. Acta 1762 (2006) 181–190.
[41] E. Blachly-Dyson, J. Song, W.J. Wolfgang, M. Colombini, M. Forte, Multicopy suppressors of phenotypes resulting from the absence of yeast VDAC encode a VDAC-like protein, Mol. Cell. Biol. 17 (1997) 5727–5738.
[42] A. Lee, X. Xu, E. Blachly-Dyson, M. Forte, M. Colombini, The role of yeast VDAC genes on the permeability of the mitochondrial outer membrane, J. Membr. Biol. 161 (1998) 173–181.
[43] H. Kmita, O. Stobienia, J. Michejda, The access of metabolites into yeast mitochondria in the presence and absence of the voltage dependent anion selective channel (YVDAC1), Acta Biochim. Pol. 46 (1999) 991–1000.
[44] N. Antos, M. Budzińska, H. Kmita, An interplay between the TOM complex and porin isoforms in the yeast *Saccharomyces cerevisiae* mitochondria, FEBS Lett. 500 (2001) 12–16.

[45] H. Kmita, N. Antos, M. Wojtkowska, L. Hryniewiecka, Processes underlying the upregulation of Tom proteins in *S. cerevisiae* mitochondria depleted of the VDAC channel, J. Bioenerg. Biomembr. 36 (2004) 187–193.
[46] H. Galganska, M. Budzinska, M. Wojtkowska, H. Kmita, Redox regulation of protein expression in *Saccharomyces cerevisiae* mitochondria: possible role of VDAC, Arch. Biochem. Biophys. 479 (2008) 39–45.
[47] C.F. Mello, R. Sultana, M. Piroddi, J. Cai, W.M. Pierce, J.B. Klein, D.A. Butterfield, Acrolein induces selective protein carbonylation in synaptosomes, Neuroscience 147 (2007) 674–679.
[48] J. Wawryn, A. Swieciło, G. Bartosz, T. Biliński, 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 (2002) 199–202.
[49] A. Karachitos, H. Galganska, M. Wojtkowska, M. Budzinska, O. Stobienia, G. Bartosz, H. Kmita, Cu, Zn-superoxide dismutase is necessary for proper function of VDAC in Saccharomyces cerevisiae cells, FEBS Lett. 583 (2009) 449–455.
[50] A.G. Komarov, D. Deng, W.J. Craigen, M. Colombini, New insights into the mechanism of permeation through large channels, Biophys. J. 89 (2005) 3950–3959.
[51] T.K. Rostovtseva, S.M. Bezrukov, VDAC regulation: role of cytosolic proteins and mitochondrial lipids, J. Bioenerg. Biomembr. 40 (2008) 163–170.
[52] K. Chen, S.R. Thomas, A. Albano, M.P. Murphy MP, J.F.J. Keaney, Mitochondrial function is required for hydrogen peroxide-induced growth factor receptor transactivation and downstream signaling, J. Biol. Chem. 279 (2004) 35079–35086.
[53] S. Elchuri, T.D. Oberley, W. Qi, R.S. Eisenstein, L. Jackson Roberts, H. Van Remmen, C.J. Epstein, T.T. Huang, CuZnSOD deficiency leads to persistent and widespread oxidative damage and hepatocarcinogenesis later in life, Oncogene 24 (2005) 367–380.
[54] M. Huizing, W. Ruitenbeek, F.P.V. DePinto, U. Wendel, F.J. Trijbels, L.M. Smit, H.J. ter Laak, L.P. van den Heuvel, Deficiency of the voltage-dependent anion channel: a novel cause of mitochondriopathy, Pediatr. Res. 39 (1996) 760–765.
[55] V. De Pinto, A. Messina, A. Schmid, S. Simonetti, F. Carnevale, R. Benz, Characterization of channel-forming activity in muscle biopsy from a porin-deficient human patient, J. Bioenerg. Biomembr. 32 (2000) 585–593.
[56] L.J. Martin, Mitochondriopathy in Parkinson disease and amyotrophic lateral sclerosis, J. Neuropathol. Exp. Neurol. 65 (2006) 1103–1110.
[57] F. Tomasello, A. Messina, L. Lartigue, L. Schembri, C. Medina, S. Reina, D. Thoraval, M. Crouzet, F. Ichas, V. De Pinto, F. De Giorgi, Outer membrane VDAC1 controls permeability transition of the inner mitochondrial membrane in cellulo during stress-induced apoptosis, Cell Res. 19 (2009) 1363–1376.
[58] T. Drakulic, M.D. Temple, R. Guido, S. Jarolim, M. Breitenbach, P.V. Attfield, I.W. Dawes, Involvement of oxidative stress response genes in redox homeostasis, the level of reactive oxygen species, and ageing in *Saccharomyces cerevisiae*, FEMS Yeast Res. 5 (2005) 1215–1228.
[59] A. Goerlach, P. Klappa, T. Kietzmann, The endoplasmic reticulum: folding, calcium homeostasis, signaling, and redox control, Antioxid. Redox Signal. 8 (2006) 1391–1418.
[60] V. Shoshan-Barmatz, A. Israelson, The voltage-dependent anion channel in endoplasmic/sarcoplasmic reticulum: characterization, modulation and possible function, J. Membr. Biol. 204 (2005) 57–66.
[61] N. Antos, O. Stobienia, M. Budzińska, H. Kmita, Under conditions of insufficient permeability of VDAC1, external NADH may use the TOM complex channel to cross the outer membrane of *Saccharomyces cerevisiae* mitochondria, J. Bioenerg. Biomembr. 33 (2001) 119–126.
[62] J.C. Lai, W. Tan, L. Benimetskaya, P. Miller, M. Colombini, C.A. Stein, A pharmacologic target of G3139 in melanoma cells may be the mitochondrial VDAC, Proc. Natl Acad. Sci. U. S. A. 103 (2006) 7494–7499.
[63] E. Simamura, H. Shimada, T. Hatta, K. Hirai, Mitochondrial voltage-dependent anion channels (VDACs) as novel pharmacological targets for anti-cancer agents, J. Bioenerg. Biomembr. 40 (2008) 213–217.