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VDAC activation by the 18 kDa translocator protein (TSPO), implications for apoptosis

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Abstract The voltage dependent anion channel (VDAC), located in the outer mitochondrial membrane, functions as a major channel allowing passage of small molecules and ions between the mitochondrial inter-membrane space and cytoplasm. Together with the adenine nucleotide translocator (ANT), which is located in the inner mitochondrial membrane, the VDAC is considered to form the core of a mitochondrial multiprotein complex, named the mitochondrial permeability transition pore (MPTP). Both VDAC and ANT appear to take part in activation of the mitochondrial apoptosis pathway. Other proteins also appear to be associated with the MPTP, for example, the 18 kDa mitochondrial Translocator Protein (TSPO), Bcl-2, hexokinase, cyclophylin D, and others. Interactions between VDAC and TSPO are considered to play a role in apoptotic cell death. As a consequence, due to its apoptotic functions, the TSPO has become a target for drug development directed to find treatments for neurodegenerative diseases and cancer. In this context, TSPO appears to be involved in the generation of reactive oxygen species (ROS). This generation of ROS may provide a link between activation of TSPO and of VDAC, to induce activation of the mitochondrial apoptosis pathway. ROS are known to be able to release cytochrome *c* from cardiolipins located at the inner mitochondrial membrane. In addition, ROS appear to be able to activate VDAC and allow VDAC mediated release of cytochrome c into the cytosol. Release of cytochrome c from the mitochondria forms the initiating step for activation of the mitochondrial apoptosis pathway. These data provide an understanding regarding the mechanisms whereby VDAC and TSPO may serve as targets to modulate apoptotic rates. This has implications for drug design to treat diseases such as neurodegeneration and cancer.

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Introduction

The voltage dependent anion channel (VDAC), located in the outer mitochondrial membrane, also known as porin, functions as the major channel allowing passage of nucleotides, ions, including Ca^{2+}, and various other metabolites between the mitochondrial intermembrane space and cytoplasm (Shoshan-Barmatz and Gincel 2003; Colombini 2004; Shoshan-Barmatz et al. 2006). VDAC is not only found in mammals, but also in amoeba and yeast (Slocinska et al. 2004). Regarding the tertiary structure of VDAC, several lines of experimental evidence suggest that the VDAC structure comprises a transmembrane β-barrel formed by 13- (Colombini, 2004) or 16- (De Pinto 2003) β-strands and an amphipathic N-terminal α-helix assigned by different mappings as being exposed to the cytoplasm (De Pinto 2003), crossing the membrane (Colombini 2004), or lying on the membrane surface (Reymann et al. 1995).

VDAC and ANT

Together with the adenine nucleotide translocator (ANT), which is located in the inner mitochondrial membrane, the VDAC is considered to form the core of a mitochondrial multiprotein complex, the mitochondrial permeability transition pore (MPTP; Verrier et al. 2003; Veenman and Gavish 2006; Veenman et al. 2007). The MPTP has been

previously described to be involved in the control of mitochondrial membrane permeabilization (Verrier et al. 2003). In this context, the ANT and VDAC were found to present targets for numerous pro-apoptotic mitochondrial membrane permeabilization inducers (Verrier et al. 2003). Complexes formed by VDAC and ANT generally are considered to play important roles in apoptosis induction via the mitochondrial apoptosis pathway (Vyssokikh and Brdiczka 2003). The mitochondrial apoptosis pathway involves an increase of outer mitochondrial membrane permeability that leads to the release of various proteins from the intermembrane space into the cytoplasm, including apoptogenic molecules such as cytochrome *c*, Smac/Diablo, HtrA2 (Omi), AIF, and DNaseG (Wang 2001; Green and Evan 2002; Tsujimoto and Shimizu 2007). In the presence of ATP (dATP), cytochrome *c* binds to Apaf-1 and triggers its oligomerization, after which pro-caspase-9 is recruited and undergoes autoactivation. The protein complex comprising cytochrome *c*, Apaf-1, and caspase-9 is called the "apoptosome". Thus, an increase of outer mitochondrial membrane permeability via the VDAC is considered to be essential for the mitochondrial apoptosis pathway (Desagher and Martinou 2000; Tsujimoto 2003).

Some controversy regarding this subject exists. For example, studies with yeast cells by Shimizu et al. (2000) indicated that VDAC is required for mitochondrial apoptosis induction, while ANT is not. Also anti-VDAC antibodies can inhibit mitochondrial membrane potential ($\Delta\Psi_m$) transition, suggesting an important role of the VDAC in mitochondrial membrane permeability and apoptosis induction (Shimizu et al. 2001). In contrast, while VDAC generally is considered to play an important role in mitochondrial-dependent cell death, experiments using VDAC-null mice suggest that VDAC is dispensable for mitochondrial-dependent cell death, reserving a more important role for ANT in this respect (Halestrap et al. 2002; Baines et al. 2007). Furthermore, in vitro studies with mouse fibroblasts indicate that detachment of Hexokinase II from mitochondria implicated ANT in the induction of apoptosis, but not VDAC (Chiara et al. 2008). Thus, the above studies indicate that some controversies regarding involvement of VDAC and ANT in apoptosis exist. Sade et al. (2004) using thymocytes appear to have resolved some of these controversies. These authors used the ability of dexamethasone to initiate cytochrome c-dependent processing of caspase-9 and the activation of caspase-3 to trigger apoptotic damage (Sade et al. 2004). This pathway could be inhibited by blocking either the VDAC or the ANT component of the MPTP. For example, using a pharmacological modifier of VDAC, dithiocyanatostilbene-2,2-disulfonic acid (DIDS), implicated the VDAC in loss of the $\Delta\Psi_m$, cytochrome c release, processing of caspase-9 and caspase-3, and nuclear damage. Inhibiting the ANT also blocked dexamethasone-induced apoptosis, including caspase-3 processing and nuclear damage, but not the mitochondrial efflux of cytochrome c (Sade et al. 2004). Thus, two separable, but connected events regarding apoptosis inductions can be recognized. The first event is a VDAC related increase in permeability of the mitochondrial outer membrane leading to VDAC-regulated efflux of cytochrome c and initial processing of caspase-9. The second event is ANT-dependent caspase-3 processing and apoptotic damage to cells (Sade et al. 2004).

VDAC and other proteins

In addition to VDAC and ANT, the MPTP may interact with several other proteins, which can be associated with the MPTP from the cytosol, the inner and outer mitochondrial membranes, and from the inter-membrane space, as listed below (McEnery et al. 1992; Gavish et al. 1999; Beurdeley-Thomas et al. 2000; Schwarzer et al. 2002; Verrier et al. 2003; Roman et al. 2006; Veenman et al. 2007). For example proteins located in the outer mitochondrial membrane, such as the 18 kDa Translocator Protein (TSPO), formerly named the peripheral-type benzodiazepine receptor (PBR), PBR-associated protein 1 (PRAX-1), and PBR-associated protein 7 (PAP7). MPTP associated proteins from the cytosol include, actin, hexokinases, glycerol kinase, and mitochondrial heat shock protein 70 (mtHSP70). From the inner mitochondrial membrane, cyclophylin D (CypD) interacts with the MPTP. From the inter-membrane space, creatine kinase interacts with the MPTP. The MPTP may also interact with proteins of the Bcl-2 family, including Bax and Bid (Verrier et al. 2003; Shoshan-Barmatz et al. 2006; Tsujimoto and Shimizu 2007; Veenman et al. 2007). Some of these proteins have been well studied for their involvement in apoptosis and interactions with VDAC.

Proteins of the Bcl-2 family are well known for their anti-apoptotic activity (Tsujimoto and Shimizu 2007). For example, mitochondrial membrane permeability is directly regulated by proteins of the Bcl-2 family (Tsujimoto 2003; Adams and Cory 2001). In particular, Bcl-2 is capable of blocking VDAC and ANT activity (Shimizu et al. 1998). Also hexokinases are considered to play a role in the regulation of VDAC function. For example, in vitro and in vivo studies have shown that hexokinase-I and hexokinase-II can down regulate the mitochondrial apoptosis pathway via direct interaction with the VDAC (Azoulay-Zohar et al. 2004). Hexokinase-I interacts directly with VDAC to induce channel closure and prevent the release of cytochrome *c*, in this way providing protection against apoptotic death (Azoulay-Zohar et al. 2004; Zaid et al. 2005). It has also been shown that binding of hexokinase-II

to mitochondria can inhibit the induction of cell death (Pastorino et al. 2005). It was found recently that two cytoplasmic domains in the VDAC1 protein are required for interaction with hexokinase-I and for hexokinase-I-mediated protection against cell death via inhibiting release of cytochrome *c* (Abu-Hamad et al. 2008). Cyclophylin D has also been studied in relation to the pro-apoptotic activity of VDAC (Tsujimoto and Shimizu 2007). Cyclophylin D can be found in complex with VDAC and ANT (Crompton et al. 1998). Studies using cyclophylin D deficient mice have suggested that cyclophylin D is involved in $\Delta\Psi_m$ transition (Nakagawa et al. 2005; Baines et al. 2005; Basso et al. 2005; Schinzel et al. 2005). However, it appears that cyclophylin D dependent $\Delta\Psi_m$ transition is more important for necrosis than for apoptosis (Nagawaka et al. 2005; Baines et al. 2005; Tsujimoto and Shimizu 2007).

VDAC and TSPO

Interactions between VDAC and TSPO are also considered to play a role in apoptotic cell death (Veenman et al. 2004; Levin et al. 2005). TSPO and VDAC where first described to be closely associated in rat kidney by McEnery et al. (1992). These interactions between VDAC and TSPO were considered to be potentially important for TSPO functions (Gavish et al. 1999), although the mechanisms were enigmatic at that time. It was suggested that interactions between TSPO and VDAC may affect TSPO binding characteristics (Joseph-Liauzun et al. 1997; Veenman et al. 2002). TSPO formerly was known as the PBR (see also above), or isoquinoline binding protein (IBP), recently however, by consensus within the diverse field of TSPO research, the name TSPO was introduced to best reflect its functional capabilities (Gavish et al. 1999; Veenman and Gavish 2006; Papadopoulos et al. 2006; Veenman et al. 2007). In most prokaryotes investigated so far TSPO and VDAC have not been detected together. However, in *Legionella pneumophila*, TSPO and VDAC like proteins appear to be expressed together, putatively to induce apoptosis in their human host cells (Khemiri et al. 2008). For some years, interactions between TSPO and VDAC are considered to play a role in the activation of the mitochondrial apoptosis pathway (Levin et al. 2005; Veenman et al. 2007; Kugler et al. 2008). In particular, it has been suggested that the TSPO may activate the MPTP to open and cause transition of the $\Delta\Psi_m$, leading to initiation of the mitochondrial apoptosis pathway (Levin et al. 2005; Veenman et al. 2007).

To study a potential role of TSPO in apoptosis, we genetically modified C6 glioma cells (Levin et al. 2005). With knockdown of the TSPO, by stable transfection of the TSPO cDNA in the antisense orientation, we acquired 50% reductions in TSPO ligand binding and protein expression, both in the mitochondrial and whole cell fractions. Apoptosis assays showed a 60% reduction in the level of apoptosis in TSPO knockdown cells. Furthermore, knockdown of the TSPO appeared to prevent induction of apoptosis by the antineoplastic agent, erucylphosphocholine (ErPC). In addition, TSPO knockdown prevented processing of the caspase 3 component of the apoptosis cascade by the erucylphosphocholine congener, erucylphosphohomocholine (ErPC3). Thus, these results suggested that enhanced TSPO expression in cancer cells may provide a mechanism to increase apoptotic rates of cancer cells (Levin et al. 2005).

Our TSPO knockdown with genetic manipulation suggested that TSPO interacts with the MPTP, including the VDAC, to activate the mitochondrial apoptosis pathway (Levin et al. 2005). To further study this aspect of TSPO function, i.e. interactions with the VDAC, we investigated the significance of opening of the MPTP for ErPC3-induced apoptosis. In particular, we studied whether the TSPO ligands, PK 11195 and Ro5 4864, could affect potential MPTP opening by ErPC3, and whether these ligands could prevent induction of the mitochondrial apoptosis pathway by ErPC3. Furthermore, we measured cytochrome *c* release, and caspase-9 and -3 activation in this paradigm (Kugler et al. 2008). With this study we found that the human glioblastoma cell lines, U87MG, A172, and U118MG express the TSPO, the VDAC, and the ANT. This study also reported that ErPC3-induced apoptosis was inhibited by the MPTP blocker cyclosporin A, and in a concentration-dependent manner by the TSPO ligands, PK 11195 and Ro5 4864. Furthermore, this study showed that PK11195 and Ro5 4864 inhibited collapse of the $\Delta\Psi_m$, cytochrome *c* release, and caspase-9 and -3 activation caused by ErPC3 treatment. Thus, this study revealed that the TSPO ligands PK 11195 and Ro5 4864 can inhibit the pro-apoptotic function of ErPC3 by blocking its capacity to cause a collapse of the $\Delta\Psi_m$ and consequently preventing initiation of the mitochondrial apoptosis pathway (Kugler et al. 2008). From these studies we concluded that the TSPO may serve to open the VDAC component of the MPTP in response to anti-cancer drugs such as ErPC3.

VDAC, TSPO, and drug development

Due to its apoptotic functions, potentially via its interactions with VDAC, the TSPO has become a target for drug development (Veenman and Gavish 2000, 2006; Galiegue et al. 2003; Veenman et al. 2007). In support of this endeavor we have found that TSPO ligands can prevent neurodegenerative effects of kainic acid (Veenman et al.

2002). These findings were supported by later studies applying TSPO ligands to different animal models for neurodegeneration (Ryu et al. 2005; Veiga et al. 2005; Amitani et al. 2008). Also in a model for brain trauma we found that TSPO ligands can prevent progressing neuronal death around the injured brain area (Soustiel et al. 2007). Thus, our studies suggest that TSPO ligands with anti-apoptotic effects potentially may serve for future treatments of secondary brain damage following brain trauma and also for treatment of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease (Veenman et al. 2007; Maniv et al. 2007). As TSPO ligands with anti-apoptotic effects potentially may serve as drugs against neurodegeneration, TSPO ligands with pro-apoptotic effects may serve as anti-cancer agents. Also anti-cancer agents that do not bind directly to TSPO, such as ErPC and ErPC3, were shown to induce their apoptotic effects via the TSPO and MPTP (Jendrossek et al. 2001; Kugler et al. 2004, 2005, 2008; Levin et al. 2005; Shandalov et al. 2007).

VDAC, TSPO, and reactive oxygen species

For several decades, the generation of reactive oxygen species (ROS) has been considered to take part in neurodegeneration due to disease and trauma (for reviews, see for example, Dröge and Schipper 2007; Swerdlow 2007). Also in cancer, ROS are considered to play various important roles (Blanchetot and Boonstra 2008; Lau et al. 2008). In addition, several studies have implicated the TSPO in the role of ROS in neurodegeneration and cancer (Veenman and Gavish 2006; Papadopoulos et al. 2006). Based on these considerations, we approached the possibility that the generation of ROS by ErPC3 may be a way to affect TSPO and VDAC function (Kugler et al. 2006). Indeed, we found that ErPC3 is capable of producing ROS, as for example indicated by oxidation of cardiolipins as presented in Fig. 1. For this study, we applied nonyl acridine orange (NAO) to demonstrate oxidative damage to cardiolipins, as described previously by Kluza et al. (2002) and Petrosillo et al. (2003). As cardiolipins are primarily located at the mitochondrial inner membrane (Smith et al. 2008), this indicates that ROS generation caused by ErPC3 takes place at the mitochondria. This apparent generation of ROS at the mitochondrial level by ErPC3, as measured by oxidation of cardiolipins, could be blocked by the specific TSPO ligand, PK 11195, suggesting an essential role of TSPO in this process of ROS generation by ErPC3 (Fig. 1). We also found that the same procedure of application of ErPC3 activates the mitochondrial apoptosis pathway, while application of PK 11195 and Ro5 4864 blocks this activation (Kugler et al. 2008). Thus, our assumption that

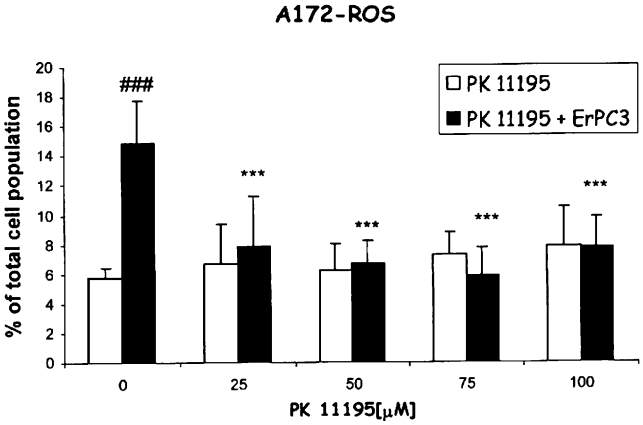

Fig. 1 Fractions of total numbers of cells showing oxidation of cardiolipin, indicative of mitochondrial ROS levels, as assayed with the aid of NAO in A172 glioma cells that were treated for 24 h with 30 μM ErPC3 and/or PK 11195 at various concentrations. *White columns* indicate cells treated with PK 11195. *Black columns* indicate cells co-treated with PK 11195 and ErPC3. (n=9 per group); ###$p<$ 0.001, for ErPC3 treatment only vs. untreated control; ***$p<0.001$, for ErPC3 plus PK 11195 treatments vs. ErPC3 treatment only

ROS may play a role in apoptosis induced by ErPC3 via activation of TSPO appears to be a valid one.

The data discussed above show that the application of ErPC3 causes activation of the various stages of the mitochondrial apoptosis pathway, including: (1) generation of ROS at the mitochondrial level, as determined with oxidative damage to cardiolipins, (2) opening of the MPTP as evidenced by detection of $\Delta\Psi_m$ transition, (3) cytochrome c release, (4) caspase 9 activation, (5) caspase 3 activation, (6) induction of DNA fragmentation, (7) blebbing of cells indicative of apoptosis. In short, ErPC3 activated the mitochondrial apoptosis pathway (Levin et al. 2005; Kugler et al. 2004, 2005, 2008). All these stages of activation of the mitochondrial apoptosis pathway could be blocked by the TSPO ligands, PK 11195 and Ro5 4864, and also by TSPO knockdown (Levin et al. 2005; Shandalov et al. 2007; Kugler et al. 2008; Shoukrun et al. in press). This indicated that TSPO activates the initiation of the mitochondrial apoptosis pathway.

Potential mechanisms of TSPO and VDAC interactions

An important question remaining was how TSPO can activate VDAC to initiate apoptosis. Data provided by the literature suggest that the intermediary agent between TSPO and VDAC may be provided by ROS. Such studies are suggesting that mitochondrial ROS generation, as we found to occur by ErPC3 via TSPO, may serve for the activation of VDAC to initiate the mitochondrial apoptosis pathway. For example, exposure of liver mitochondria to succinate, which results in $\Delta\Psi_m$ related ROS generation,

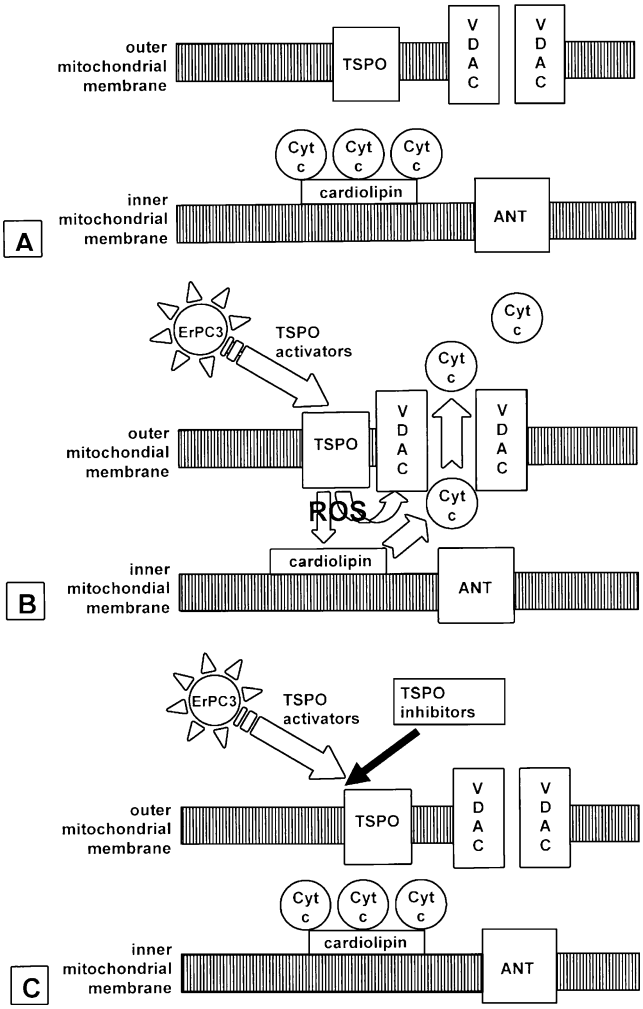

Fig. 2 TSPO and VDAC driven initiation of the mitochondrial apoptosis pathway. **A** In this presentation, when not activated, TSPO and VDAC are not conducive for cytochrome *c* release. **B** Activation of TSPO (for example by ErPC3) leads to ROS generation, resulting in release of cytochrome *c* from cardiolipins at the inner mitochondrial membrane and formation of a pore via activation of the VDAC, allowing cytochrome *c* to enter the cytosol. **C** Application of TSPO ligands blocking TSPO activity, indicated as "inhibitors" in the figure (or TSPO knockdown) inhibits this ROS generation, restoring TSPO and VDAC to their inactive states

was also found to result in a release of cytochrome *c*, while the outer mitochondrial membrane remained intact under these conditions (Nishimura et al. 2001; Petrosillo et al. 2003). This was accompanied by a loss of cardiolipin, which is typically bound to the inner mitochondrial membrane, indicating that cytochrome c is dissociated from the cardiolipin (Schlame et al. 2000; Petrosillo et al. 2003). The ROS induced cytochrome c release could be inhibited by the VDAC blocker, DIDS (Shafir et al. 1998; Petrosillo et al. 2003). As mentioned, cytochrome *c* release from mitochondria is the initial step of the mitochondrial apoptosis pathway. The release of cytochrome c in the study of Petrosillo et al. (2003) was not accompanied by mitochondrial swelling or loss of the $\Delta\Psi_m$. In other studies it was also found that ROS induced alterations of VDAC and/or ANT can induce mitochondrial membrane permeability selective for cytochrome *c* release, without causing further mitochondrial damage (Madesh and Hajnoczky 2001; Le Bras et al. 2005). It has been suggested that increase of VDAC pore size, for example via phosphorylation by protein kinase A, can be a mechanism of allowing cytochrome c release (Banerjee and Ghosh 2006). It has also been suggested that assemblage of VDAC molecules into groups of up to 20 or even larger aggregates, including hexagonal packing, may play a role in cytochrome c release (Goncalves et al. 2007). ROS induced upregulation of the VDAC as a cytochrome c releasing channel can be prevented by the ROS chelator, epigallocatechin (EGCG; Jung et al. 2007). In this process of cytochrome c release from the mitochondria as an initiating step of the mitochondrial apoptosis pathway, interactions between ROS and VDAC, as well as ROS and cardiolipins, have come to be recognized to play central roles (Nomura et al. 2000; Madesh and Hajnoczky 2001; Nishimura et al. 2001;

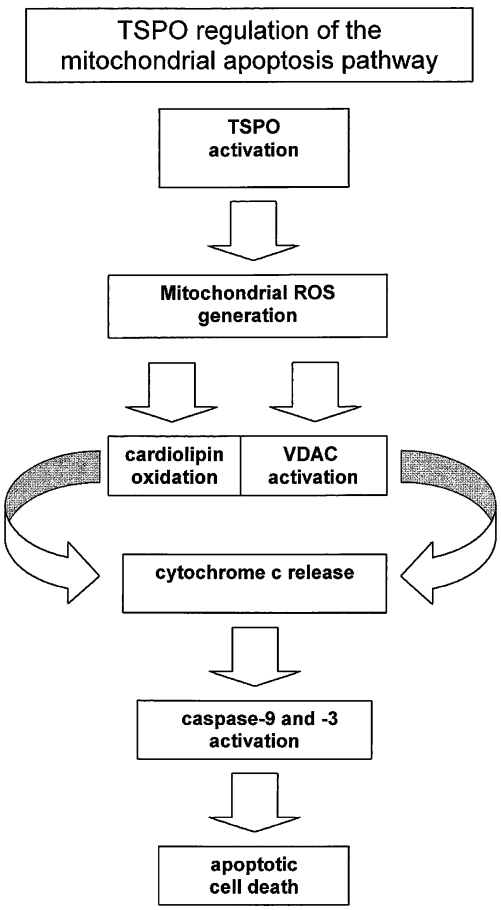

Fig. 3 Diagram of cytochrome c release due to ROS generation following activation of TSPO and subsequent initiation of the mitochondrial apoptosis pathway

MCMillin and Dowhan 2002; Petrosillo et al. 2003; Jiang et al. 2008). Cytochrome c release can also be blocked by ADP (Petrosillo et al. 2003). We suggest that TSPO's strategic location, not only in association with VDAC but also with ANT, is an important factor in this process. Interestingly in this respect, we found that knockdown of ANT also prevented apoptotic effects of ErPC (Held-Kuznetsov et al. 2005; Kuznetsov et al. 2005). This may suggest that TSPO activation by ErPC3 may not only lead to ROS generation, activating the mitochondrial apoptosis pathway via VDAC, but may also lead to involvement of ANT, including its ATP transport to the cytosol, in activation of the mitochondrial apoptosis pathway.

We hypothesize that TSPO's close association with VDAC (McEnery et al. 1992; Gavish et al. 1999) may help to ensure that ROS generated via TSPO actually can affect the VDAC. Also reported groupings of TSPO molecules around VDAC, potentially including TSPO polymerization (Papadopoulos et al. 1994; Golani et al. 2001; Veenman et al. 2002, 2007; Lacapère and Papadopoulos 2003), may aid to enhance the concentration of ROS generated by TSPO in the proximity of the VDAC.

As a consequence of the studies mentioned above, we imply that ROS generation under the control of TSPO may participate in the activation of the two step process of cytochrome c dissociation from cardiolipins and subsequent release via formation of a pore or channel due to VDAC activation (Fig. 2). Subsequently, the mitochondrial release of cytochrome c activates the mitochondrial apoptosis pathway (Fig. 3). We suggest that some TSPO ligands can inhibit ROS generation by TSPO, which is normally induced by ErPC3, and consequently prevent the ROS induced dissociation of cytochrome *c* from cardiolipins and subsequent release of cytochrome c via VDAC activation (Fig. 2). We consider the possibility that ligands inhibiting TSPO activity, resulting in reduced ROS generation, also reduce interactions between TSPO and VDAC, which in turn reduces the size of the pore provided by activation of the VDAC (Fig. 2). This reduction of VDAC activation then presents a second stop on cytochrome c release from the mitochondria in addition to the prevention of cytochrome *c* dissociation from cardiolipins. Further studies are needed to clarify the exact mechanisms whereby VDAC activation leads to release of cytochrome c from the mitochondria.

Conclusions

The VDAC is generally considered to be a component of the mitochondrial channel complex, named MPTP. Among the various components of this complex, the TSPO appears to play a specific role by its interactions with VDAC. Recent data suggest that ROS generation via TSPO can activate the mitochondrial apoptosis pathway by driving out cytochrome c via oxidation of cardiolipins and VDAC related increase in permeability of the mitochondrial outer membrane leading to VDAC-regulated efflux of cytochrome c. These data provide an understanding regarding the mechanisms whereby VDAC and TSPO may serve as targets to modulate apoptotic rates. This has implications for drug design to treat diseases such as neurodegeneration and cancer.

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