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Themed Section: Mitochondrial Pharmacology: Featured Mechanisms and Approaches for Therapy Translation

# REVIEW ARTICLE

# Pharmacological modulation of mitochondrial ion channels

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The field of mitochondrial ion channels has undergone a rapid development during the last three decades, due to the molecular identification of some of the channels residing in the outer and inner membranes. Relevant information about the function of these channels in physiological and pathological settings was gained thanks to genetic models for a few, mitochondria-specific channels. However, many ion channels have multiple localizations within the cell, hampering a clear-cut determination of their function by pharmacological means. The present review summarizes our current knowledge about the ins and outs of mitochondrial ion channels, with special focus on the channels that have received much attention in recent years, namely, the voltage-dependent anion channels, the permeability transition pore (also called mitochondrial megachannel), the mitochondrial calcium uniporter and some of the inner membrane-located potassium channels. In addition, possible strategies to overcome the difficulties of specifically targeting mitochondrial channels versus their counterparts active in other membranes are discussed, as well as the possibilities of modulating channel function by small peptides that compete for binding with protein interacting partners. Altogether, these promising tools along with large-scale chemical screenings set up to identify new, specific channel modulators will hopefully allow us to pinpoint the actual function of most mitochondrial ion channels in the near future and to pharmacologically affect important pathologies in which they are involved, such as neurodegeneration, ischaemic damage and cancer.

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## Abbreviations

CGS7184, Ethyl1-[[(4-chlorophenyl)amino]oxo]-2-hydroxy-6-trifluoromethyl-1*H*-indole-3-carboxy-late; CIC, intracellular chloride channel; CPP, cell penetrating peptide; CSA, cyclosporin A; DPC, diphenyl carbonate; EMRE, essential MCU regulator; GSK-3, glycogen synthase kinase 3; G3139, phosphorothioate oligodeoxyribonucleotide; Hsp, heat shock protein; IMAC, inner membrane anion channel; IMM, inner mitochondrial membrane; HK, hexokinase; MCU, mitochondrial calcium uniporter; MMC, mitochondrial mega-channel; NS1619, (1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-1,3-dihydro-2*H*-benzimidazol-2-one; OMM, outer mitochondrial membrane; OSCP, oligomycin sensitivity conferral protein; PAP-1, 5-(4-phenoxybutoxy)psoralen; PDAC, pancreatic ductal adenocarcinoma; PM, plasma membrane; PTP, permeability transition pore; ROMK, renal outer medullary potassium channel; RR, ruthenium red; RyR1, ryanodine receptor; SITS, stilbene isothiocyanate sulfonic acid; TPP, triphenylphosphonium; TRPC, transient receptor potential cation channel; UCP, uncoupling protein; VDAC, voltage-dependent anion channel

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## Introduction

A relatively recent and certainly noteworthy development in the health sciences is the emergence of 'mitochondrial medicine', based on the recognition of the key role mitochondria play in many physiological processes whose alteration contributes to disease, such as metabolism, $Ca^{2+}$ handling, redox signalling and cell death (see recent, excellent reviews on this topic, e.g. Heller *et al.*, 2012; Smith *et al.*, 2012; Edeas and Weissig, 2013; Szeto *et al.*, 2014; Milane *et al.*, 2015; Guzman-Villanueva and Weissig, 2017; Masgras *et al.*, 2017).

An important opportunity for intervention to modulate these processes is offered by mitochondrial ion channels (reviews on mitochondrial channels; Brini *et al.*, 2017; Citi *et al.*, 2017; Krabbendam *et al.*, 2018; Mammucari *et al.*, 2018; O'Rourke, 2007; Ponnalagu and Singh, 2017; Szabo and Zoratti, 2014; Szewczyk *et al.*, 2009). These channels are especially important, at least in the contexts of cancer (Figure 1) (for reviews, see Leanza *et al.*, 2013a, 2014b; Madamba *et al.*, 2015; Peruzzo *et al.*, 2016; Mazure, 2017; Szabo and Leanza, 2017; Shoshan-Barmatz *et al.*, 2017b), neurodegeneration (Rodriguez *et al.*, 2013; Rao *et al.*, 2014; Kalani *et al.*, 2018) and ischaemia (Balderas *et al.*, 2015; Testai *et al.*, 2015b; Smith *et al.*, 2017). In the present review, we discuss the recent developments in the field of mitochondrial ion channels, especially from the point of view of their pharmacological targeting. Specifically modulating members of this varied population may well be a rewarding approach, in particular in the case of cancer due to the major roles mitochondria play in cancer cell metabolism and in cell death. Pharmacological manipulation of mitochondrial channels may lead to cell death independently of upstream elements of the apoptotic cascade, such as **Bax/Bak/Bcl-2** expression or p53 status, and alterations in signalling pathways (Fulda *et al.*, 2010; Leanza *et al.*, 2013a, 2014a,b, 2017). Expression levels of ion channels in general and of mitochondrial channels in particular may vary from one cell type to another, and between healthy and diseased or activated cells. Examples of drastic variations of this type are provided by the **two-pore acid-sensitive potassium channel, $K_{2P}$9.1 (TASK-3)** (Mu *et al.*, 2003) and intracellular anion-selective **CIC** channels, which also change localization and function in malignant cells (e.g. Peretti *et al.*, 2015; Tasiopoulou *et al.*, 2015). Silencing $K_{2P}$9.1 channels affects mitochondrial parameters and induces apoptosis in melanoma cells (Nagy *et al.*, 2014). In the case of the potassium-selective **$K_v$1.3** channel, a higher expression correlated with greater sensitivity to chemotherapeutic treatment (Leanza *et al.*, 2014b).

## Multiple localizations of some of the ion channels found in mitochondria

When taking into account the possible pharmacological modulation of mitochondrial ion channels, one important distinction must be immediately made between mitochondria-specific and multiple-location channels. In fact, a few channels, such as the mitochondrial calcium uniporter (MCU), the inner membrane anion channel (IMAC), the magnesium-transporting Mrs2 and the uncoupling protein (UCP), are specific to mitochondria. However, most of the other known ones reside in the plasma membrane as well, and possibly also elsewhere, as detailed in Table 1. These channels include the voltage-dependent anion channel (VDAC), the big-, intermediate- and small-conductance calcium-dependent potassium channels (**$K_{Ca}$1.1** ($BK_{Ca}$), **$K_{Ca}$3.1(IKCa)** and **$K_{Ca}$2.1** (SKCa)] as well as the voltage-dependent $K^+$ channels Kv1.3, **Kv1.5** and **Kv7.4**, the two-pore channel $K_{2P}$9.1, the ATP-dependent $K^+$ channel (KATP; **$K_{ir}$3.4**) and the intracellular chloride channels **CIC-4** and **CIC-5** (for summarizing review, e.g. Szabo and Zoratti, 2014). The mechanisms underlying multiple targeting are being investigated (Singh *et al.*, 2013; Kilisch *et al.*, 2015; von Charpuis *et al.*, 2015; Sole *et al.*, 2016) but are still unclear in most cases. The mechanisms accounting for different localizations of proteins in general vary and may include differences among isoforms (e.g. due to

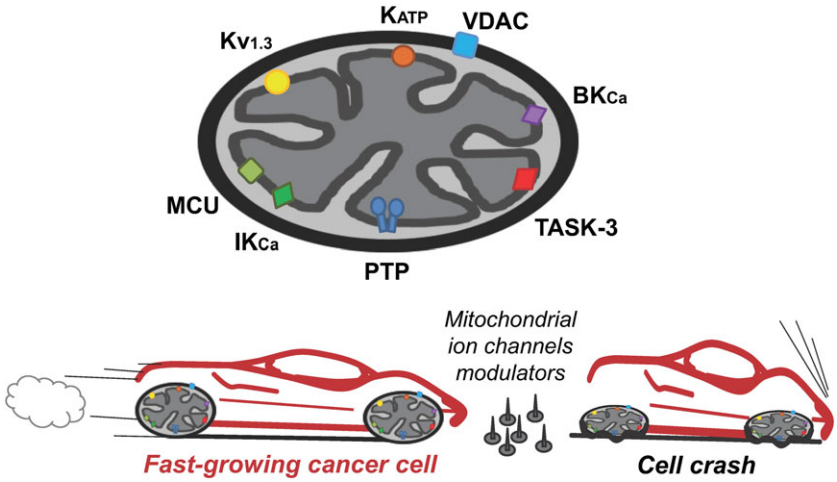



**Figure 1**
A cartoon illustrating the main mitochondrial ion channels discussed in this review and their impact on cancer.

## Table 1

Mitochondrial channels in non-mitochondrial locations

| Channel | Location[a] | Proposed functions[b] | References[b] |
|---|---|---|---|
| VDAC | Plasma membrane | Cell volume regulation<br>Apoptosis<br>ATP release | Thinnes (1992, 2014, 2015)<br>Jakob *et al.* (1995)<br>Bathori *et al.* (1999, 2000) |
| VDAC | Endosomes | – | Reymann *et al.* (1998) |
| VDAC | Endo/sarcoplasmic reticulum | ATP transport<br>SR/ER-Mito $Ca^{2+}$ transport/signalling | Jurgens *et al.* (1995)<br>Shoshan-Barmatz *et al.* (1996); Shoshan-Barmatz and Israelson (2005) |
| BKCa (SLO1, $K_{Ca}1.1$) | Plasma membrane | Integration of cell signalling | Singh *et al.* (2012); Yu *et al.* (2016); Latorre *et al.* (2017) |
| BKCa (SLO1, $K_{Ca}1.1$) | ER membrane | – | Ma *et al.* (2007); Cox *et al.* (2014) |
| BKCa (SLO1, $K_{Ca}1.1$) | Nuclear envelope | Control of nuclear $Ca^{2+}$ signalling | Singh *et al.* (2012); Li *et al.* (2014) |
| BKCa (SLO1, $K_{Ca}1.1$) | Lysosomal membrane | Control of lysosomal $Ca^{2+}$ | Wang *et al.* (2017a,b); Sterea *et al.* (2018) |
| IKCa ($K_{Ca}3.1$, KCNN4) | Plasma membrane | Cell proliferation, differentiation, migration<br>Control of NO synthesis (in vascular epithelia) | Sforna *et al.* (2018); Zhan *et al.* (2018)<br>Grgic *et al.* (2005); Sheng and Braun (2007); Ruggieri *et al.* (2012); Ohya and Kito (2018) |
| SKCa ($K_{Ca}2.x$) | Plasma membrane | Control of electrical excitability | Yang *et al.* (2015); Kshatri *et al.* (2018) |
| SKCa ($K_{Ca}2.x$) | ER membrane | Control of ER $Ca^{2+}$ homeostasis | Kuum *et al.* (2012, 2015); Richter *et al.* (2016); Honrath *et al.* (2017a) |
| Kv7.4 | Plasma membrane | Control of electrical excitability<br>Smooth muscle function<br>Regulation of vascular tone | Chang *et al.* (2018)<br>Miceli *et al.* (2008)<br>Martelli *et al.* (2013) |
| SLO2.1 ($K_{Na}1.2$) | Plasma membrane | Control of electrical excitability and of synaptic transmission<br>Anaesthetic preconditioning | Kameyama *et al.* (1984)<br>Wojtovich *et al.* (2016) |
| Kv1.3 | Plasma membrane | Control of voltage and $Ca^{2+}$ fluxes | Cahalan and Chandy (2009); Zhao *et al.* (2015); Perez-Verdaguer *et al.* (2016); Chandy and Norton (2017); Serrano-Albarras *et al.* (2018) |
| Kv1.3 | ER and Golgi | – | Sole *et al.* (2009); Zhu *et al.* (2014) |
| Kv1.3 | Nuclear envelope | Regulation of nuclear transmembrane potential | Jang *et al.* (2015) |
| Kv1.5 | Plasma membrane | $O_2$ sensing | Comes *et al.* (2013) |
| TASK-3 ($K_{2P}9.1$) | Plasma membrane | Cell excitability (background current) | Zuzarte *et al.* (2007); Kilisch *et al.* (2015) |
| ROMK2 ($K_{ir}1.1b$) | Plasma membrane (renal epithelia) | Ion homeostasis | Zhou *et al.* (1994); Yoo *et al.* (2005); Angsanakul and Sitprija (2013); Frindt *et al.* (2013); Welling (2016) |
| KATP[c] | Plasma membrane | Control of transmembrane potential | Noma (1983) |
| KATP[c] | Nuclear envelope | Control of nuclear $Ca^{2+}$ 'waves' | Quesada *et al.* (2002) |
| KATP[c] | ER | Control of $Ca^{2+}$ load and dynamics | Ashrafpour *et al.* (2008); Salari *et al.* (2015) |
| TRPC3 | Plasma membrane | Mechanosensitive $Ca^{2+}$ signalling<br>Cellular $Ca^{2+}$ homeostasis | Mizoguchi and Monji (2017); Yamaguchi *et al.* (2017); Tiapko and Groschner (2018) |

*continues*

**Table 1**
(Continued)

| Channel | Location[a] | Proposed functions[b] | References[b] |
|---|---|---|---|
| RyR | Sarcoplasmic reticulum | $Ca^{2+}$ dynamics<br>Excitation/contraction coupling | Allard (2018)<br>Treves *et al.* (2017) |
| RyR | Nuclear envelope | – | Gerasimenko and Gerasimenko (2004); Marius *et al.* (2006); Zheng *et al.* (2012) |
| IP3R | Endoplasmic reticulum | $Ca^{2+}$ signalling<br>Signal integration<br>ER-mitochondria communication | Foskett *et al.* (2007); Bustos *et al.* (2017); Kania *et al.* (2017) |
| IP3R | Nuclear envelope | $Ca^{2+}$ signalling | Mak and Foskett (1994); Stehno-Bittel *et al.* (1995); Gerasimenko and Gerasimenko (2004); Mak *et al.* (2013) |
| IP3R | Plasma membrane (low levels) | $Ca^{2+}$ entry | Mayrleitner *et al.* (1995); Dellis *et al.* (2006) |
| CIC-4 | Plasma membrane | – | Peretti *et al.* (2015) |
| CIC-4 | Nuclear envelope | – | Domingo-Fernandez *et al.* (2017) |
| CIC-1 | Plasma membrane | Volume regulation<br>Cell migration<br>Metastasis | Valenzuela *et al.* (2000)<br>Novarino *et al.* (2004)<br>Wang *et al.* (2012); Setti *et al.* (2013); Peretti *et al.* (2015) |
| CIC-1 | Nuclear envelope | – | Valenzuela *et al.* (1997) |

[a]Refers to subcellular compartments. Organ-, tissue- or cell type-specific or signalling-dependent expression is not addressed. Due to cellular membrane traffic and protein flux, integral PM proteins are expected to be found also in the ER, Golgi (anterograde transport) and endosomes, lysosomes (degradative retrograde transport). Thus, for example, $IK_{Ca}$, which has a rapid turnover, is abundant in lysosomes (Balut *et al.*, 2010). The presence in these compartments is therefore not highlighted here, except if evidence exists of a functional presence in the organellar membrane and in the case of VDAC, a largely mitochondrial channel for which it constitutes confirmation of its presence also in the PM.
[b]Examples are given.
[c]$K_{ir}$/SUR assemblies.

alternative splicing), 'piggybacking' other proteins, the formation of different heteromers [e.g. in the case of $K_{Ca}1.1$ ($BK_{Ca}$) channels; Chen *et al.*, 2009], post-translational modifications such as, for example, phosphorylation or myristoylation, interactions with structures such as, for example, 'scaffolds', the cytoskeleton or, in membranes, 'lipid rafts'.

The channel populations residing in different compartments in general have different tasks, roles and/or substrates, and it may therefore be useful to pharmacologically target them specifically in mitochondria or elsewhere. Unfortunately, the art of subcellular targeting is still in its infancy – mitochondrial targeting is by far the most developed – so that little information is available comparing the effects of inhibiting a given channel in one subcellular compartment or another. A partial exception is provided by the plasma membrane, since some of the ion channels in it are inhibited by membrane-impermeant toxins. The clearest example may be that of potassium-selective channel $K_v1.3$: selective block of the plasma membrane population by peptide toxins impairs cell proliferation and migration (e.g. Chhabra *et al.*, 2014; Aissaoui *et al.*, 2018), while selective inhibition of the mitochondrial population by permeant, mitochondriotropic psoralenic compounds precipitates cell death (Leanza *et al.*, 2017). It ought also to be mentioned that mitochondria themselves may differ in structure, properties, functions and proteic composition depending on their location within the cell (e.g. see Diaz *et al.*, 1999, 2000; Riva *et al.*, 2005; Boengler *et al.*, 2009; Baseler *et al.*, 2011; Asemu *et al.*, 2013; Kasumov *et al.*, 2013; Hollander *et al.*, 2014; Fedorovich *et al.*, 2017), not to mention cell type and age. It is also important to mention that not all mitochondrial ion channels have been described/found in all tissues, but they are certainly observable in healthy tissues, not only in pathological cells (cell lines). In the present review, we illustrate our current knowledge on the drugs identified so far that act on mitochondrial ion channels and comment on some of the strategies that can be useful to target specifically the mitochondria-located channels.

## Mitochondrial outer membrane (OMM) channels

### *VDAC*

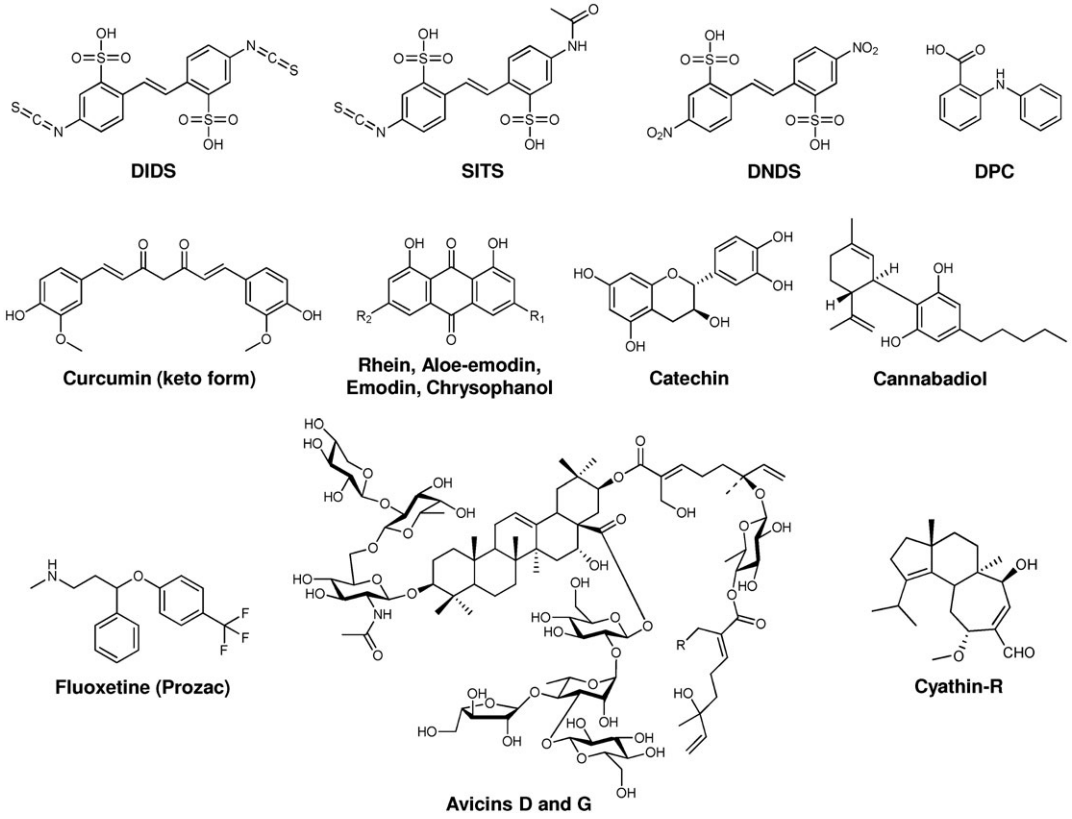
The VDAC, or 'mitochondrial porin', is the most extensively studied mitochondrial channel (rev.s: Szabo and Zoratti, 2014; Magri *et al.*, 2018; Shoshan-Barmatz *et al.*, 2018). The

most abundant and most investigated of the three mammalian isoforms (VDAC1, VDAC2 and VDAC3) (for recent review, see, e.g. Messina *et al.*, 2012) is VDAC1, which is present both in the OMM and in the PM (Bathori *et al.*, 2000; De Pinto *et al.*, 2010), in endosomes (Reymann *et al.*, 1998) and in the sarco/endoplasmic reticulum (Jurgens *et al.*, 1995; Shoshan-Barmatz *et al.*, 1996) (Table 1). The effects of the various modulators have nearly always been automatically attributed to their action on mitochondrial porin(s). The possibility of a contribution by populations located elsewhere has rarely been adequately explored.

VDAC1 is a β-barrel composed of 19 β-strands and of an N-terminal mobile α-helical segment (for recent review, see, e.g. Zeth and Zachariae, 2018). The latter contains the major binding sites for ions and other proteins (Caterino *et al.*, 2017; Magri and Messina, 2017). As the functions of the N-terminal peptide and the network of interactions were progressively characterized, VDAC1 has progressed from a more or less inert 'molecular sieve' in the OMM to a dynamic participant in a host of cellular processes. One is that of allowing and regulating the passage of $Ca^{2+}$ ions through the OMM (Gincel *et al.*, 2001; Bathori *et al.*, 2006) and at ER/mitochondria contact sites (Hajnoczky *et al.*, 2002; Rapizzi *et al.*, 2002). The binding of Bcl-xL to the N-terminal segment may modulate this flux. Mitochondrial $Ca^{2+}$ overload may induce cell death, in which VDAC1 is implicated in various other ways as well. In particular, VDAC can oligomerize in a $Ca^{2+}$-driven process, with the involvement of the N-terminus, and oligomers are proposed to be implicated in the release of pro-apoptotic factors such as cytochrome c and apoptosis-inducing factor (AIF) (for recent review, see Shoshan-Barmatz *et al.*, 2017a). Furthermore, VDAC1 regulates cell death due to its interactions with anti-apoptotic members of the Bcl-2 family (i.e. Bcl2 and Bcl-xL) and with **hexokinase** (HK) (Shimizu *et al.*, 2000; Arbel and Shoshan-Barmatz, 2010).

Various chemical compounds interact with and alter the activity of VDAC1 and may eventually be exploited for therapy in the context of VDAC-related diseases (Figure 2). The first VDAC blocker to be identified was Konig's polyanion, a 1:2:3 copolymer of methacrylate, maleate and styrene that acts at rather low concentrations (27 $\mu g \cdot mL^{-1}$ polyanion) (Colombini *et al.*, 1987). The general anion channel inhibitors **DIDS**, **SITS**, H(2) DIDS, 4,4′-dinitrostilbene-2,2′-disulfonic acid (DNDS) and diphenyl carbonate (DPC) were also shown to interact with VDAC1 and to decrease its conductance in electrophysiological experiments with bilayer-reconstituted VDAC1 (Thinnes *et al.*, 1994; Ben-Hail and Shoshan-Barmatz, 2016). Furthermore, ubiquinone specifically binds to VDAC1 through its quinone-head ring (Murai *et al.*, 2017).

The phosphorothioate oligodeoxyribonucleotide G3139 (**oblimersen**) was shown to induce rapid flickering of the VDAC1 channel activity and even its closure at 1 μM




## Figure 2

Chemical structure of some VDAC modulators. For further information, see text.

concentration without affecting the respiration complexes, the adenine nucleotide translocator or the ATP synthase (Tan *et al*., 2007; Stein and Colombini, 2008). G3139 interferes with metabolite flow through VDAC1 (for review, see, e.g. Klasa *et al*., 2002). G3139 targets the first six codons of Bcl-2 mRNA and is successfully used in anticancer treatments in combination with other therapeutic agents (including chemotherapy and radiotherapy), in tumour types ranging from chronic lymphocytic leukaemia beta cell lymphoma to breast cancer and many solid tumours (Kamal *et al*., 2014). The relevance of the block of VDAC1 activity for the anticancer effect of G3139 is not clear. In general, closure of VDAC would lead to an overall lowering of the cell energy metabolism, subsequently triggering apoptosis.

Other compounds that decrease the conductance of VDAC are avicins, a class of plant stress-induced metabolites of triterpenoids displaying selective pro-apoptotic and cytotoxic activity in cancer cells, as well as antioxidant and anti-inflammatory properties (see, e.g. Haridas *et al*., 2007). Avicins however stimulate tumour cell death via multiple mechanisms, as they target various cellular components in addition to VDAC, such as tubulin and topoisomerase. They increase the OMM permeability to cytochrome *c* by inhibiting respiration and by reducing the efficiency of antioxidant systems, leading to a hypersensitivity of mitochondria to oxidative stress. In particular, mitochondria are the main targets of avicin D and avicin G, which can induce apoptotic cell death *via* intrinsic and extrinsic pathways but also autophagic programmed cell death due to depletion of cell energy. Avicins could thus be of value as chemical agents for the treatment and/or prevention of malignancy (Wang *et al*., 2010).

The activity of VDAC can also be manipulated by other plant-derived molecules. **Cannabidiol**, from the *Cannabis* species, has strong *in vitro* anti-tumour effects in numerous cancer cells types (Massi *et al*., 2013), and was shown to act on VDAC (Rimmerman *et al*., 2013). **Curcumin**, a component of *Curcuma longa* with anti-inflammatory and anti-tumour activity, has also been shown to affect VDAC function by interacting with its N-terminal domain, at least *in vitro* (Tewari *et al*., 2015). Chrysophanol, emodin, rhein, aloe-emodin and catechin, identified as the bioactive components of the herb *Rheum officinale Baill* and able to induce apoptosis in many human cancer cell lines, were shown to target VDAC-1 through $Thr^{207}$ and the N-terminal region of the protein (Li *et al*., 2017). However, a direct effect on channel conductance and behaviour has still not been proven.

The list of chemicals that directly modify VDAC1 activity by decreasing channel conductance also includes **fluoxetine** (Prozac) (Nahon *et al*., 2005; Thinnes, 2005), a clinically used antidepressant drug, that also inhibits the opening of the mitochondrial permeability transition pore, the release of cytochrome c, and protects against **staurosporine**-induced apoptotic cell death. Lastly, cyathin-R, a cyathane diterpenoid, was shown to decrease both channel conductance and cancer growth, by promoting apoptosis even in Bax/Bak-deficient cells (Huang *et al*., 2015). Cyathin-R also induced VDAC1 oligomerization, and apoptosis was found to be inhibited by VDAC1-interacting molecules, such as DIDS and DIDS analogues ($H_2$DIDS, SITS and DPC). These drugs decrease the channel conductance (Thinnes *et al*., 1994) and counteract apoptosis at the early stage, putatively by diminishing VDAC1 oligomerization and thus preventing cytochrome c release to the cytosol (Keinan *et al*., 2010).

The above examples point to an important role for VDAC in the regulation of apoptosis; however in some cases, inhibition/decrease of its activity by pharmacological means leads to apoptosis (e.g. G3139), while in other cases, the same modulation of VDAC activity results in protection against cell death (e.g. Prozac). In fact, the role of VDAC activity/oligomerization in OMM permeabilization (MOMP)-induced apoptosis seems to be rather complex. Bax and t-Bid have been proposed to take part in the formation of OMM pores in apoptotic cells by assembling heteromeric complexes with VDAC (Tajeddine *et al*., 2008). Other studies however indicate a cooperative role of Bak and Bax and VDAC2, rather than of VDAC1, in MOMP (see, e.g. Cheng *et al*., 2003 and for review, Lauterwasser *et al*., 2016), and also the involvement of other outer membrane 'receptors' for pro-apoptotic proteins, including cardiolipin (for recent review, see, e.g. Veresov and Davidovskii, 2014). This may explain why cells lacking all VDAC isoforms were found to be still capable of undergoing apoptosis (Baines *et al*., 2007). In addition, the interaction of VDAC with other partners such as with the glycolytic enzyme hexokinase is also important, as it gives a proliferative advantage to cancer cells (see below).

Unfortunately, one drawback in this field is the absence of VDAC isoform-specific pharmacological agents. VDAC2 (Gattin *et al*., 2015) and VDAC3 (Checchetto *et al*., 2014) also form ion channels, although the latter one with small conductance. It is worthwhile to mention that a recent work reported the synthesis of an arsenate-based fluorescent probe, which can preferentially target the mitochondrial VDAC2, this channel being a member of the membrane-bound vicinal dithiol protein class (Yang *et al*., 2018). Even if isoform-specific small molecule inhibitors are not available, as an alternative strategy for specific targeting of VDAC isoforms, peptides copying specific VDAC sequences that can modulate the interaction with various pro- and anti-apoptotic proteins (see below) can be designed and can be therefore useful to modulate a specific VDAC-related function. Of course this approach would require an extension of our knowledge on the isoform-specific interaction partners (if there are specific ones) for all three isoforms.

## *Other mitochondrial outer membrane channels*

Beside VDAC isoforms, the OMM also harbours a few other channels such as an unidentified inward rectifying potassium channel (**$K_{ir}$**) (Fieni *et al*., 2010) and CIC-4, a member of the intracellular chloride channel family (Ponnalagu *et al*., 2016a; Ponnalagu and Singh, 2017). CICs are **indanyloxyacetic acid-94** (IAA-94)-sensitive, but several mitochondrial CIC family members are present also in the endoplasmic reticulum (Ponnalagu *et al*., 2016b) making it difficult to delineate the function of mitochondrial CICs by pharmacological means. The existence of CICs and $K_{ir}$ channels, both small-conductance channels, in the OMM challenges the traditional view that the outer membrane forms an unspecific size-exclusion filter for the flux of small

hydrophilic molecules (Becker and Wagner, 2018). In yeast mitochondria, the recent identification of three novel ion channels in the OMM with unknown substrate specificity (Kruger *et al.*, 2017) points to the same conclusion (Checchetto and Szabo, 2018). Whether homologues of the yeast OMM channels also operate in mammalian OMM is still an open question as is the pharmacology of these channels.

## Inner membrane ion channels

### *The permeability transition pore*

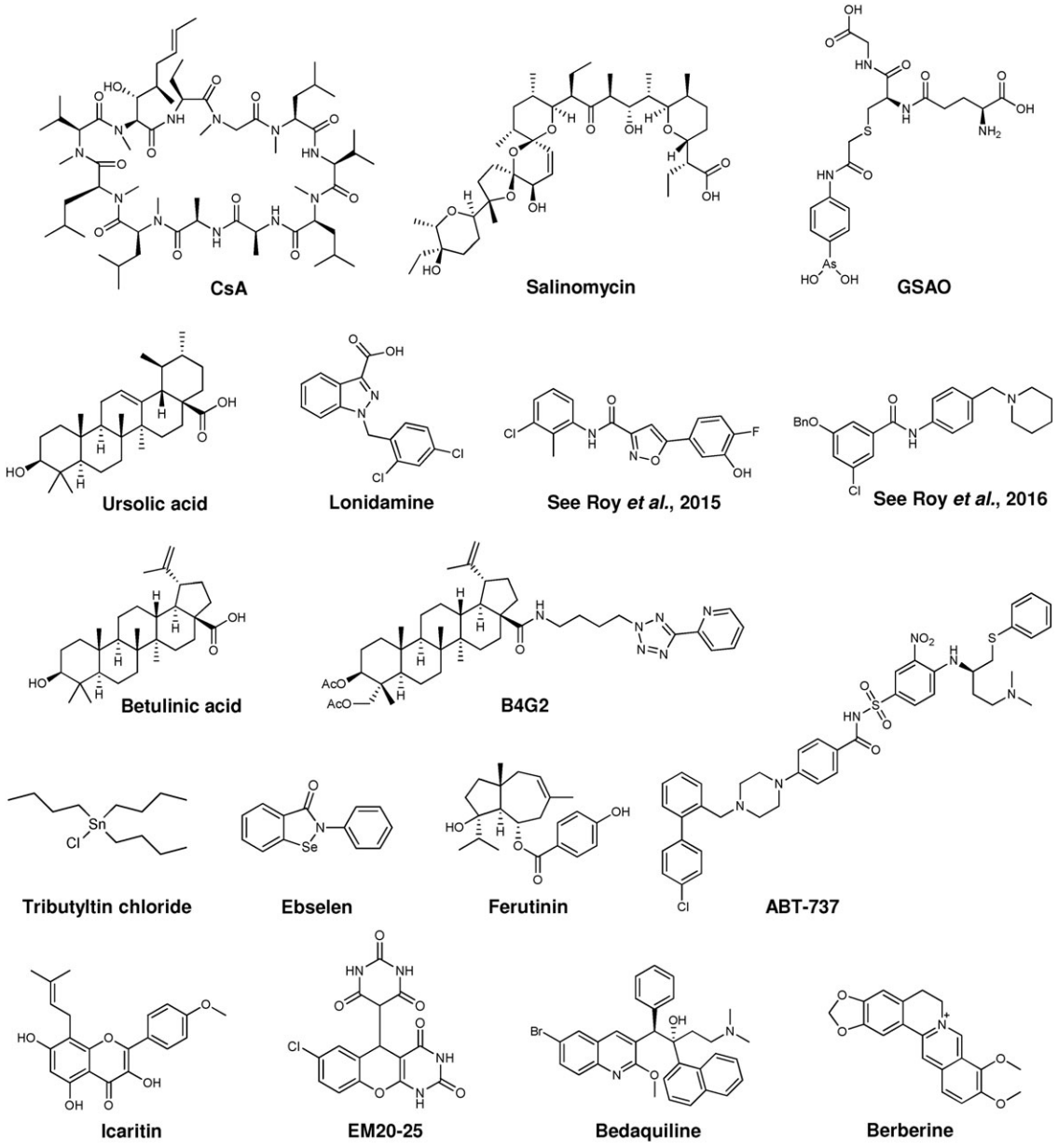
The permeability transition is a well-known process that occurs in mitochondria: an increased permeability to solutes of the inner mitochondrial membrane (IMM) caused by the opening of the permeability transition pore (PTP) (Zoratti and Szabo, 1995; Bernardi *et al.*, 2015). PTP is a 1.3 nS conductance unspecific channel located in the IMM whose opening induces depolarization, loss of ionic homeostasis and block of respiratory chain activity and ATP synthesis. The expression 'permeability transition' to describe these phenomena (considered as an aspecific, lipid-perturbation effect) was used for the first time in the late seventies by Haworth and Hunter (1979). The discovery of the ability of **cyclosporin A** (CsA) to inhibit PTP in classical bioenergetics experiments (Crompton *et al.*, 1988) and the observation of a CsA-sensitive 1.3 nS ion channel in patch clamp experiments on mitoplasts, that is, mitochondria devoid of OMM (Szabo and Zoratti, 1991), completely changed the perspectives concerning the permeability transition (PT). The observed channel, the so-called mitochondrial mega-channel (MMC), reproduced all known pharmacological features of the PTP: inhibition by CsA, adenine nucleotides, $Mg^{2+}$, acidic pH and reducing agents, induction by $Ca^{2+}$ (Szabo and Zoratti, 2014). PT, that thanks to these studies could be ascribed to a pore (PTP), changed its 'status' from being a supposed *in vitro* artefact or lipid perturbation to an important physiopathological process involved in cell death, apoptosis resistance in cancer cells, oxidative stress, anoxia and ischaemia followed by reperfusion, just to name a few (for reviews, see, e.g. Di Lisa and Bernardi, 2006; Brenner and Moulin, 2012; Rasola and Bernardi, 2014; Leanza *et al.*, 2014b).

Despite the fact that the role of PTP in mitochondrial physiology was intensively studied in the last decades in different pathophysiological contexts, the structure and molecular identity of PTP is still highly debated (Biasutto *et al.*, 2016; Giorgio *et al.*, 2018), making difficult the 'smart design' of a structure-based specific channel modulator. As to date, the scientific community is converging towards the idea that PTP is formed by dimers of the $F_OF_1$ ATP synthase (Alavian *et al.*, 2014; Beutner *et al.*, 2017; Bonora *et al.*, 2013; Carraro *et al.*, 2014; Giorgio *et al.*, 2013; He *et al.*, 2017), even though the exact mechanism and the site and mode of the actual pore formation is still unclear. In this respect, as well as regarding the possibility of designing specific drugs, the strategies undertaken, involving site-directed mutagenesis combined with functional assays (Giorgio *et al.*, 2017; Antoniel *et al.*, 2018), might turn out to be extremely useful. Indeed, strong support in favour of the identification of the ATP synthase with PTP/MMC is the finding that modulation of MMC activity directly recorded by patch clamp in the native mitochondrial inner membrane by protons was altered in a single point mutant of the oligomycin sensitivity conferral protein (OSCP) subunit of the ATP synthase complex (Antoniel *et al.*, 2018). In addition, subunits e, g and the first transmembrane segment of subunit b have recently been shown to contribute to channel formation in yeast, by combining multiple gene deletion with electrophysiology (Carraro *et al.*, 2018).

Given the central role of the PTP in pathophysiological contexts, considerable effort was made in the field to discover new, direct modulators to treat disorders, even in the absence of a clear molecular identity. Pharmacological targeting of PTP is not straightforward, since no bona fide pore blockers are available. In fact, even the action of the relatively specific CsA, which is effective at sub-μM concentrations, is indirect, as it is mediated by cyclophilin D, whose expression level varies among different cells. Furthermore, not only is cyclophilin D expression important but also its ratio with F-ATPase OSCP subunits: considering that normally there are more F-ATP synthase complexes than cyclophylin D molecules in the cells, most of the PTP complexes present are expected to be insensitive to CsA treatment (Bernardi *et al.*, 2015). CsA inhibits calcineurin and thus acts as an immunosuppressant (Griffiths and Halestrap, 1995). Therefore, several new, calcineurin-indifferent cyclophilin D inhibitors have been developed over the past 20 years. The most promising are sanglifehrin A (Clarke *et al.*, 2002), 9-(*N*-methyl-*L*-isoleucine)-cyclosporin A (Zulian *et al.*, 2014) and MeAla(3) EtVal(4)-cyclosporin (Tiepolo *et al.*, 2009). Recently, other factors have also been shown to modulate PTP by targeting cyclophilin D, such as **oestrogen receptor β** (Burstein *et al.*, 2018), **isoxazoles** (Roy *et al.*, 2015) and n-phenylbenzamides (Roy *et al.*, 2016). A virtual chemical screening identified several compounds that were able to bind to cyclophilin D with a $K_D$ of <100 nM (Park *et al.*, 2017). Synthetic compounds from the diarylquinoline and organotin families instead target the c-ring of the F-ATPase and strongly inhibit the enzyme (Pagliarani *et al.*, 2016). A member of these families, tributyltin, induces mitochondrial swelling, which has long been associated with the PT, but is CsA-insensitive, at least according to some authors (see, e.g. Gogvadze *et al.*, 2002).

Several different classes of compounds acting at sites that do not involve the PTP pore itself have been characterized for their ability to antagonize the mitochondrial permeability transition in an indirect way (Figure 3). Among these substances are gasotransmitters (NO-donors, $H_2S$-donors and Co-donors) (for review, see Andreadou *et al.*, 2015) and antioxidants (Javadov and Karmazyn, 2007), just to name a few classes. Altogether, all the above-mentioned inhibitors, even though by an indirect effect, were proven to affect PTP activity in various systems. Some of them might represent good starting points for the design of more specific pharmacological agents able to counteract those degenerative diseases where PTP opening plays a crucial role.

Conversely, several PTP inducers with different chemical structures and displaying distinct mechanisms of PTP activation are promising agents for the treatment of cancer. Indeed, some of these compounds are already in clinical trials; others have been tested *in vitro* in tumour cell lines or




## Figure 3

Chemical structure of some modulators of the permeability transition pore. For further information, see text.

*in vivo* in preclinical models for different neoplasms. Some of these molecules are mastoparan-like peptides (Jones *et al.*, 2008), 4-(*N*-(Sglutathionylacetyl)amino)phenylarsonous acid (Elliott *et al.*, 2012), ursolic acid (Lu *et al.*, 2014), **betulinic acid** (Fulda *et al.*, 1999; Potze *et al.*, 2015), B4G2 (an hydroxybetulinic acid derivative) (Yao *et al.*, 2015), triterpenoid derivatives (Laszczyk, 2009; Serafim *et al.*, 2014), curcumin (Qiu *et al.*, 2014), lonidamine (Lena *et al.*, 2009), **ABT-737** (a BH3 mimetic) (Yu *et al.*, 2015), the $K^+/H^+$ antiporter salinomycin (Manago *et al.*, 2015; Qin *et al.*, 2015), berberine (Shen *et al.*, 2014), ebselen (Pavon *et al.*, 2015), the gold complex AUL-12 (Chiara *et al.*, 2012), icaritin (Zhou *et al.*, 2015), EM20-25 (Milanesi *et al.*, 2006) and ferutinin (Ilyich *et al.*, 2018). It has to be stressed that in most cases, possible side effects can be envisioned as opening of the PTP might lead to loss of mitochondrial function in healthy cells as well. Specific targeting of these molecules exclusively to tumour tissues employing various strategies (for a recent review, see Ruoslahti, 2017) is a challenge but might be a worthwhile goal to pursue.

As in the case of VDAC, one might envision not only the direct modulation of channel activity by small molecules but also the possibility to fine-tune the activity of the PTP (proposed to correspond to the ATP synthase) or of its partners/modulators (for review, see Miura and Tanno, 2012), by post-translational modifications by kinases, such as hexokinase II (HK II) (Rasola *et al.*, 2010a) or the mitochondrial **glycogen synthase kinase 3** (mGSK-3) (Rasola *et al.*,

2010a). PTP can be indirectly and negatively modulated in cancer cells by mGSK-3 phosphorylation of cyclophilin D, and mGSK-3 can in turn be inhibited by a mitochondria-located **ERK** fraction, which is normally under the control of the often dysregulated **oncogene RAS**. An active ERK in mitochondria of cancer cells was shown to lead to mGSK-3 phosphorylation, thus preventing cyclophilin D phosphorylation and in turn 'desensitizing' PTP (Rasola *et al.*, 2010a). Similarly, the PTP is inhibited when cyclophilin D is nitrosylated on specific cysteine residues (Nguyen *et al.*, 2011) or interacts with the transcription factor STAT-3 (Boengler *et al.*, 2010). Furthermore, chaperones such as heat shock protein (Hsp) 60, Hsp90 and tumour necrosis factor receptor-associated protein-1 have been demonstrated to modulate PTP activity, and these chaperones themselves can be regulated by post-translational modification (Masgras *et al.*, 2017; Rasola, 2017). Opening of the PTP can be induced also by HK II detachment from the OMM: this event can be controlled by signalling pathways that involve either the Ser/Thr kinase Akt or GSK-3, even if the mechanism accounting for this regulation is still debated (Miyamoto *et al.*, 2008; Rasola *et al.*, 2010b). Finally, some direct sites of post-translational modifications, for example, phosphorylation, acetylation and S-nitrosylation, have also been identified in the F-ATPase subunits (Bernardi *et al.*, 2015), although they may hardly offer a more specific way of intervention.

## *Mitochondrial calcium uniporter and other calcium channels*

Mitochondria play a crucial role in intracellular $Ca^{2+}$ regulation by shaping, remodelling, relaying and decoding $Ca^{2+}$ signals, due to their ability to rapidly and transiently accumulate $Ca^{2+}$ (Drago *et al.*, 2011). $Ca^{2+}$ uptake into mammalian mitochondria is efficiently blocked by low concentrations of ruthenium red (RR) and Ru360, thanks to the fact that they lead to a direct inhibition of the uniporter (Moore, 1971; Vasington *et al.*, 1972; Reed and Bygrave, 1974). The molecular identity of the protein(s) giving rise to uniporter activity was not known until the last decade. The finding that a highly $Ca^{2+}$ selective ion channel replicated all key characteristics of the mammalian mitochondrial uniporter represented a milestone towards its molecular identification (Kirichok *et al.*, 2004). Another important step was the publication of the MitoCarta database (Pagliarini *et al.*, 2008), which then provided the basis for the identification of several mitochondrial calcium uniporter complex (MCUC) components in mammals, including the central pore forming protein MCU (mitochondrial calcium uniporter) (Baughman, 2011; De Stefani *et al.*, 2011). At the current stage, in mammals, the MCUC appears to include at least the pore-forming protein MCU, an MCU paralogue (MCUb), the essential MCU regulator (EMRE), the regulatory MICU proteins and, possibly, the mitochondrial calcium uniport regulator 1 (MCUR1). In other systems, such as plants, MCUC seems simpler and consists primarily of MCU and MICU (Wagner *et al.*, 2016). Mammalian MCU activity can be regulated through its paralogue MCUb (Raffaello *et al.*, 2013), through interaction with MICU1, the first uniporter component identified (Perocchi *et al.*, 2010), by two other MICU1 isoforms, namely, MICU2 and MICU3 (Plovanich *et al.*, 2013) and by post-translational modifications (Jhun *et al.*, 2016). MICU2 forms a heterodimer with MICU1 through an intermolecular disulphide bond and closes the channel at low extramitochondrial $Ca^{2+}$ concentrations (Patron *et al.*, 2014; Petrungaro *et al.*, 2015). Currently, two models coexist that find MICU1 to act exclusively as a uniporter activator at high cytosolic $Ca^{2+}$ concentrations (Patron *et al.*, 2014) or to gradually disinhibit the uniporter with increasing $Ca^{2+}$ concentrations in the cytosol (Csordas *et al.*, 2013). Studies resolving for the first time the 3D structure of proposed pentameric MCU by a combination of NMR and electron microscopy allowed the proposal of the hypothesis to explain the requirement of the presence of EMRE in the native membrane to observe MCU activity: the outer and inner juxtamembrane helices as well as a loop region in MCU seem to be unstable regions, which may undergo conformational changes upon activation by EMRE in order to create the lateral exit path for $Ca^{2+}$ in the MCU channel (Oxenoid *et al.*, 2016). Recently, a more in-depth insight into the structure of the tetrameric MCU has been obtained, thanks to the resolution of the structure of MCU by X-ray and cryo-EM simultaneously by different groups and from different organisms (Baradaran *et al.*, 2018; Fan *et al.*, 2018; Nguyen *et al.*, 2018; Yoo *et al.*, 2018). EMRE is a metazoan-specific protein able to mediate MCU-MICU1/MICU2 dimer interaction and, as shown recently, able to regulate MCU channel activity depending on the matrix $Ca^{2+}$ concentration (Sancak *et al.*, 2013; Vais *et al.*, 2016). Furthermore, the activity of MCU can be also indirectly regulated, for example, by the uncoupling protein UCP2, as mitochondria isolated from $UCP2^{-/-}$ mice showed decreased RR-sensitive calcium uptake (Motloch *et al.*, 2016).

The importance of the correct regulation of MCU activity is underlined by the finding that patients carrying a loss-of-function mutation of MICU1 are characterized by myopathy, cognitive impairment and an extrapyramidal movement disorder (Logan *et al.*, 2014). MICU1 has recently been shown to play a role in $Ca^{2+}$ overload-induced mitochondrial PTP opening and also to be a decisive factor for adaptation to postnatal life and for tissue repair after injury of liver (Antony *et al.*, 2016). Other studies underline the importance of MCU expression/activity in the context of the regulation of metabolism in various organisms ranging from Trypanosoma to zebrafish and mice (e.g. Duchen, 2000; Huang *et al.*, 2013; Prudent *et al.*, 2013; Gorlach *et al.*, 2015; Mammucari *et al.*, 2018). The manipulation of MCU expression changed muscle function, through a novel $Ca^{2+}$-dependent mitochondria-to-nucleus signalling pathway (Mammucari *et al.*, 2015). MCU function was also shown to affect oxidative phosphorylation and to ensure correct pacemaker cell function (Wu *et al.*, 2015). MCU is overexpressed in several type of cancer cells (e.g. Davis *et al.*, 2013; Peruzzo *et al.*, 2016; Bustos *et al.*, 2017) and has been implicated in cancer-related processes, in particular in the control of migration and metastasis (Hall *et al.*, 2014; Tang *et al.*, 2015; Tosatto *et al.*, 2016; Szabo and Leanza, 2017).

Given the vast literature demonstrating the fundamental impact of calcium uptake into mitochondria for many physiological and pathological processes, it became clear that either activation (to induce calcium overload and PTP opening) or inhibition (to decrease ATP production and/or

to prevent calcium overload) of MCU might be useful in pathological settings. However, regarding pharmacological modulation of MCU, the direct inhibitors identified to date are only RR and Ru-360 (Kirichok *et al.*, 2004; De Stefani *et al.*, 2011; Wu *et al.*, 2018), which also affect other cationic channels. No specific activators are known to our knowledge. It has been proposed that a small heterocyclic molecule, 5-[(4-methylphenyl)thio]-9*H*-pyrimido[4,5-*b*]indole-2,4-diamine (AG311), retards tumour growth by activating MCU, but a direct proof is still missing (Bastian *et al.*, 2015). Likewise, the protective effect of Necrox-5 ([5-(1,1-dioxo-thiomorpholin-4-ylmethyl)-2-phenyl-1*H*-indol-7-yl]-(tetrahydro-pyran-4-ylmethyl)-amine) on myocardial damage in ischaemic heart disease has been ascribed to its ability to inhibit MCU (Thu *et al.*, 2012) but also in this case, a direct electrophysiological proof is missing. A recent work identified **mitoxantrone** as an MCU modulator by systematic chemical screening (Arduino *et al.*, 2017). Likewise, a high-throughput screening of 120 000 small-molecule compounds identified the membrane-permeant drug DS1657, an indolebutyric acid derivative (Sawada *et al.*, 2001), that dose-dependently inhibited serum-induced mitochondrial $Ca^{2+}$ influx in HEK293A cells with an $IC_{50}$ of 7 μM (Kon *et al.*, 2017). Formal proof and information about the mechanism of inhibition is lacking in the latter case. In this respect, electrophysiological lipid bilayer experiments using recombinant proteins might be useful. MCU produced in a cell-free system as well as that purified from *Escherichia coli* using His-tag, either added to the recording chamber as the purified protein or following purification and incorporation into liposomes, showed channel activity in a reproducible manner in more than 200 experiments performed in different settings (De Stefani *et al.*, 2011; Raffaello *et al.*, 2013; Patron *et al.*, 2014; Teardo *et al.*, 2017). However, a recent work using human MCU expressed in mammalian cells with FLAG-tag concluded, on the basis of only three experiments, that this protein does not form channels by itself (Wu *et al.*, 2018). Further work will be required to clarify the reasons for this discrepancy. It may be due to different conditions used for protein solubilization and purification and/or the presence of cholesterol in the latter system that is known to affect the activity of several channels (but is largely absent from the IMM) (Brini *et al.*, 2017).

Other mitochondrial $Ca^{2+}$ channels might contribute to the mediation of $Ca^{2+}$ fluxes into/out of this organelle, particularly in specialized tissues where the MCU may play a secondary role. Potential candidates mediating calcium flux include the transient receptor potential cation **TRPC3 channel** (Feng *et al.*, 2013; Wang *et al.*, 2015, 2017a,b) and the mitochondrial ryanodine receptor (m**RyR1**). A low level of RyR1 is detectable in heart mitochondria and provides rapid transport of $Ca^{2+}$ that is insensitive to ruthenium red (Beutner *et al.*, 2001, 2005). The TRPC3 channel, whose structure has been recently resolved (Tang *et al.*, 2018), is specifically inhibited by ethyl-1-(4-(2,3,3-trichloroacrylamide)phenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (Pyr3) that was shown to alter mitochondrial membrane potential and ROS production when applied together with dexamethasone (Abdoul-Azize *et al.*, 2016). However, TRPC3 and RyR1 show multiple localizations within the cell, making it difficult to ascribe the observed physiological effects to the regulation of these channels only in mitochondria.

## *Mitochondrial inner membrane potassium channels*

IMM $K^+$ channels studied by electrophysiology are the calcium-dependent channels – big-conductance potassium channel (mtBKCa) (Singh *et al.*, 2012), intermediate-conductance $K^+$ channel (mtIKCa) (De Marchi *et al.*, 2009) and small-conductance $K^+$ channel (mtSKCa) (Dolga *et al.*, 2013), voltage-gated shaker type $K^+$ channel $K_v1.3$ (Szabo *et al.*, 2005) and the ATP-dependent potassium channel (mtKATP) (Inoue *et al.*, 1991). An interesting new development in the field is the discovery that mtBKCa behaves as a mechanosensitive channel in electrophysiological experiments (Walewska *et al.*, 2018). Biochemical/genetic evidence indicates the presence of the pH-sensitive two-pore potassium channel $K_{2P}9.1$ (TASK-3) (Pocsai *et al.*, 2006; Toczylowska-Maminska *et al.*, 2014), of $K_v1.5$ (Leanza *et al.*, 2012b), of **$K_{ir}1.1$ (ROMK2)** (Foster *et al.*, 2012), of the **sodium-activated $K^+$ channel $K_{Na}1.1$ (SLO2)** (Wojtovich *et al.*, 2011; Smith *et al.*, 2018) and of $K_v7.4$ (Testai *et al.*, 2015a,b) and another pH sensitive $K^+$ channel (Kajma and Szewczyk, 2012) (for recent reviews, see, e.g. Szabo and Zoratti, 2014; Laskowski *et al.*, 2016; Augustynek *et al.*, 2017). Almost all of the above-mentioned IMM $K^+$ channels identified thus far are considered to be the mitochondrial counterparts of well-known plasma membrane (PM) channels and many of them even display multiple subcellular localizations in the ER, nucleus, Golgi and PM membranes in addition to mitochondria (Table 1) (for review, see, e.g. Laskowski *et al.*, 2016; Brini *et al.*, 2017). Nevertheless, mtKATP seems to have a different composition from its PM counterpart: a splicing variant of the renal outer medullary potassium channel (ROMK) has been proposed to form the ion-conducting subunit (Foster *et al.*, 2012) and indeed, the ROMK protein is present in the IMM (Bednarczyk *et al.*, 2018). Since ROMK apparently does not have a wide tissue-expression while mtKATP activity has been observed in various tissues, a contribution of other pore-forming proteins to mtKATP channel activity cannot, as yet, be fully excluded.

IMM $K^+$ channels have been proposed to contribute to the regulation of matrix volume, in addition to influencing the mitochondrial transmembrane potential ($\Delta\Psi m$) and $\Delta pH$, calcium transport, production of ROS and mitochondrial dynamics. Activation of a mitochondrial calcium-dependent $K^+$ channel modulates $K^+$ uptake and matrix volume and has been proposed to increase bioenergetic efficiency (Aon *et al.*, 2010). Alternatively, a protective mechanism involves activation of different IMM $K^+$ channels that induces a slight uncoupling effect that would in turn decrease energetic efficiency (Cardoso *et al.*, 2010). Activity of the evolutionarily conserved ATP-dependent $K^+$ channel mitoKATP (Garlid *et al.*, 2009; Lefer *et al.*, 2009), of BKCa (Frankenreiter *et al.*, 2017), of the voltage-gated channel $K_v7.4$ (Testai *et al.*, 2015a,b) as well as of the SK channels (Dolga *et al.*, 2013) has been linked to ischaemic preconditioning, ischaemic postconditioning and cytoprotection in general. For this latter channel, a recent work reveals that a neuroprotective mechanism involves attenuation of $[Ca^{2+}]_m$ uptake upon SK

channel activation and that respiration and complex I activity upon pharmacological activation or overexpression of mitochondrial $K_{Ca}2.2$ (SK2) channels resulted in reduced mitochondrial ROS formation (Honrath *et al.*, 2017a,b). However, in general, the exact basis of $K^+$ channel openers' cytoprotective effects still remains to be elucidated (for recent reviews, see, e.g. Honrath *et al.*, 2017a; Krabbendam *et al.*, 2018). Importantly, in the case of mtBKCa, a cGMP-dependent protective effect in the cases of acute cardiac damage and adverse long-term events that occur after myocardial infarction has been demonstrated also *in vivo*, thanks to tissue-dependent knockout of BKCa in the cardiac tissue in mice (Frankenreiter *et al.*, 2017).

Interestingly, many of the $K^+$ channels found in the IMM (in addition to the PM and other membranes) are highly overexpressed in cancer cells/tissues. For example, the two-pore leak channel $K_{2P}9.1$(TASK-3) is overexpressed five- to 100-fold in 44% of breast tumours and is also highly expressed in lung, colon and ovarian cancers (Peruzzo *et al.*, 2016). Its overexpression promotes tumour formation and confers resistance to hypoxia *in vitro*, suggesting that its up-regulation plays a pathologically important role in human breast cancer (Mu *et al.*, 2003). IKCa (also called $K_{Ca}3.1$) is expressed in almost all migrating cells and various studies point to its important role in the control of proliferation in human breast cancer, in hepatocellular carcinoma, in chronic lymphocytic leukaemia (B-CLL) and in lung cancer (for review, see Schwab *et al.*, 2012). mtIKCa is functional in HCT116 colon carcinoma and HeLa cells (Sassi *et al.*, 2010), is inhibited by **TRAM-34** and **clotrimazole** (De Marchi *et al.*, 2009) and regulates oxidative phosphorylation in pancreatic ductal adenocarcinoma cells (Kovalenko *et al.*, 2016). *In vitro* data suggest that inhibition of IKCa and likely of mtIKCa by membrane-permeant inhibitors sensitizes melanoma cells to B-Raf inhibitors, such as **vemurafenib**, and induces release of mitochondrial ROS (Bauer *et al.*, 2017).

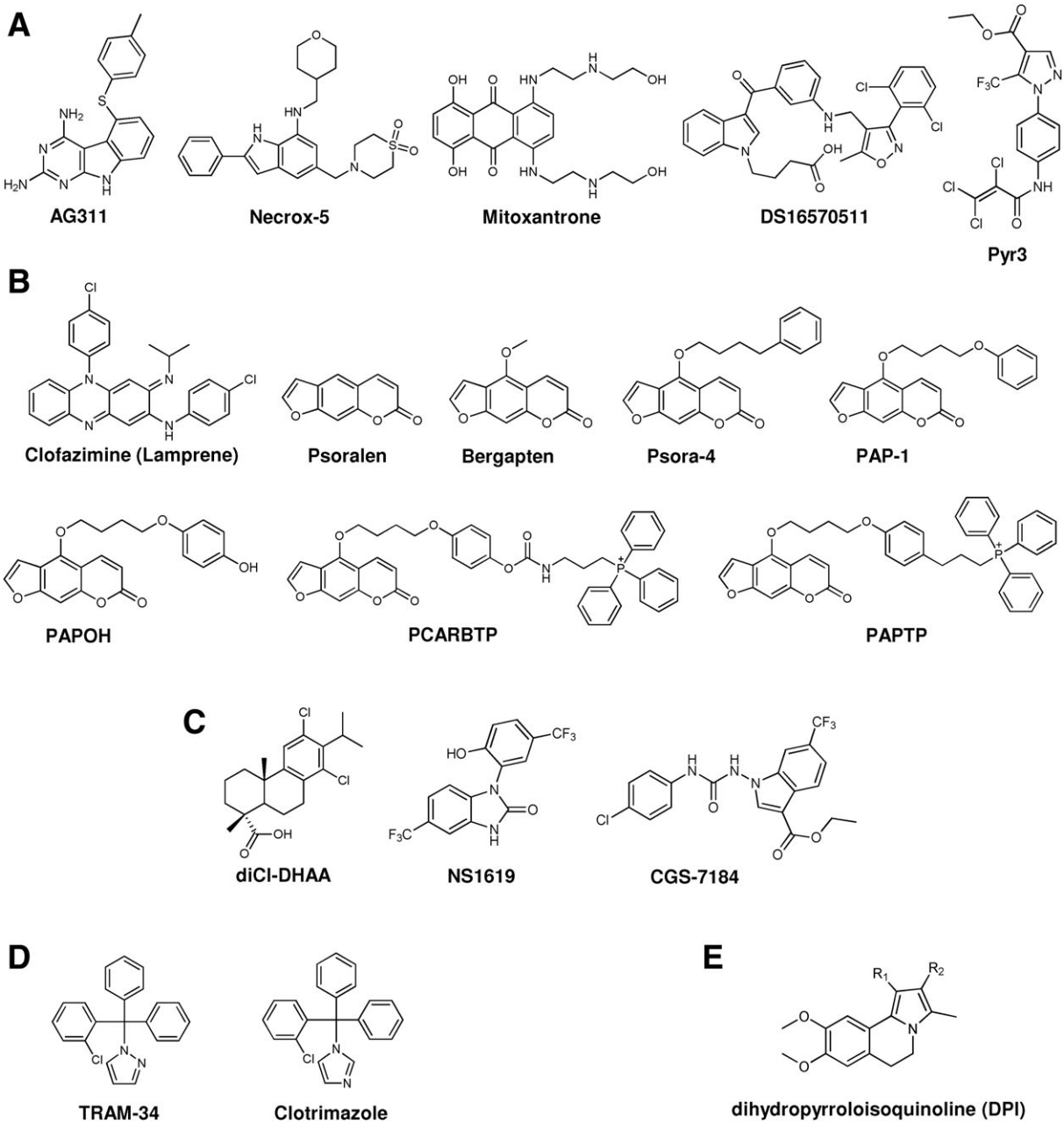
More information is available about $mtK_v1.3$: it has been demonstrated to have a crucial role in apoptosis in various cancer cells (Leanza *et al.*, 2012b; Szabo *et al.*, 2008). The $K_v1.3$ channel is overexpressed in various cancer tissues/cells (Pardo and Stuhmer, 2014) and is important for anti-tumour immunity (Eil *et al.*, 2016). Membrane-permeant inhibitors of the $K_v1.3$ channel such as **clofazimine** and psoralen derivatives act by inducing intrinsic apoptosis via the following chain of events: stopping the depolarizing $K^+$ influx causes IMM hyperpolarization, with ensuing increased ROS level, PTP activation, swelling, loss of $\Delta\psi m$, loss of cytochrome c and further ROS release (Leanza *et al.*, 2015; Checchetto *et al.*, 2018). These drugs also killed pathological cells in the absence of Bax and Bak, independently of p53 status and of Bcl-2 overexpression thanks to the direct targeting of mt function and permeability at the level of the inner membrane. *In vivo* experiments in melanoma and pancreatic ductal adenocarcinoma orthotopic models corroborated the effectiveness of Kv1.3 inhibitors and showed their selective action only on pathological cells. Specificity depends on the synergy between different factors such as high $K_v1.3$ expression and altered basal redox state in cancer cells (Leanza *et al.*, 2017).

Most of the evidence supporting the involvement of the above $K^+$ channels in protection against ischaemic/reperfusion damage (Szewczyk *et al.*, 2010; Laskowski *et al.*, 2016) or induction of apoptosis (Szabo *et al.*, 2012) is pharmacological (for a review summarizing the pharmacology of these channels, see, e.g. Szabo and Zoratti, 2014) (Figure 4). Unfortunately, other cellular targets possibly accounting for the observed effects have been identified (Augustynek *et al.*, 2017). Activators of BKCa, such as $Ca^{2+}$, diCl-DHAA (12,14-dichlorodehydroabietic acid), **NS1619**, **17-oestradiol** and hypoxia, or inhibitors of this channel like **charybdotoxin**, **iberiotoxin** and **paxillin** do not only seem to act on the mitochondrial mtBKCa channel (Szewczyk *et al.*, 2009). CGS7184 (ethyl1-[[(4-chlorophenyl)amino]oxo]-2-hydroxy-6-trifluoromethyl-1*H*-indole-3-carboxy-late), a synthetic BKCa channel opener, directly activates the ryanodine receptor calcium release (**RyR2**) channel in the sarcoplasmic reticulum (Wrzosek *et al.*, 2012). CGS7184 and CGS7181, in contrast to NS1619 and **NS004**, were also able to induce cell death in neurons (Augustynek *et al.*, 2018). Furthermore, SERCA, complex I of the respiratory chain and ATP-synthase inhibition are involved in pleiotropic effects of the BKCa channel activator NS1619 on endothelial cells (Lukasiak *et al.*, 2016). One of the most specific BKCa activators identified so far is NS11021 (*N*′-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-bromo-2-(2*H*-tetrazol-5-yl-phenyl]thiourea; however, possible intracellular off-target effects of this drug have not been studied in detail to our knowledge. KATP channel activators instead might act as uncouplers (Szewczyk *et al.*, 2010) and $K_{Ca}3.1$ (IKCa) as well as $K_{Ca}2.1$ (SKCa) modulators may well have off-target effects, similarly to those affecting BKCa channels. In the case of $mtK_{2P}9.1$ (TASK-3) channels, no highly specific modulators are available but dihydropyrrolo[2,1-α]isoquinolines compounds that are able to inhibit these $K_{2P}$ (TASK) channels could become possible candidates for developing new, selective inhibitors (Noriega-Navarro *et al.*, 2014).

One possible solution to the issue of pleotropic effects of the drugs due to multiple localization of the channels within the cells is chemical targeting of the most specific modulators of these channels to mitochondria by virtue of addition of a functional lipophilic cation (e.g. triphenylphosphonium group) that drives the accumulation of a certain drug into mitochondria (Murphy and Smith, 2007). This strategy has been successfully applied also *in vivo* in the case of $mtK_v1.3$ (see below). In summary, the relationship between mitochondrial potassium transport and diseases linked to altered mitochondrial function is still only partially explored, but the data available so far point to IMM $K^+$ channels as possible targets for therapeutic applications against various pathologies, including ischaemia and cancer, and possibly neurodegenerative diseases (see, e.g. Matschke *et al.*, 2018).

## *Inner mitochondrial membrane chloride channels*

In addition to CIC-4 in the OMM, CIC-1 (Yang *et al.*, 2009) and CIC-5 (Ponnalagu *et al.*, 2016a,b) have been located to the IMM where the latter plays a role in regulating the release of mitochondrial ROS from respiratory chain complexes. Indeed, the emerging view is that mitochondrial chloride channels also have a role in cardiac function and cardioprotection from ischaemia–reperfusion (IR) injury.




## Figure 4

Chemical structure of some modulators of other mitochondrial ion channels: (A) MCU; (B) $K_v1.3$; (C) $K_{Ca}1.1$ ($BK_{Ca}$); (D) $K_{Ca}3.1$($IK_{Ca}$); (E) $K_{2P}9.1$ (TASK-3). For further information see text and, for example, Augustynek *et al.* (2017).

Chloride intracellular channels (CIC) are non-classical ion channels lacking a signal sequence for membrane targeting. Interestingly, CIC-like proteins exist even in bacteria (Gururaja Rao *et al.*, 2017; Ponnalagu and Singh, 2017). Among CICs in mammals, CIC-1, CIC-4 and CIC-5 are abundant in the heart. In contrast to CIC-1 and CIC-4 (found in the OMM, see above), CIC-5 does not show co-localization to the endoplasmic reticulum (Ponnalagu *et al.*, 2016b). Again, as yet, no isoform-specific modulators of CICs are available (for recent review, see Ponnalagu and Singh, 2017). As to the long-studied IMAC, due to the uncertainties regarding its molecular identity, only general modulators have been identified (for review, see Ponnalagu and Singh, 2017).

## Successfully applied strategies for *in vivo* subcellular targeting of small molecule modulators of mitochondrial ion channels

Thanks to the highly negative matrix side membrane potential across the IMM, mitochondria can be massively

'loaded' with positively charged, membrane-permeant compounds, achieving concentration gradients of up to 1000-fold. This concept has been used in many studies since its inception 60 years ago (Liberman *et al.*, 1969) (for reviews, see, e.g. Ross *et al.*, 2005; Horobin *et al.*, 2007; Hoye *et al.*, 2008; Murphy, 2008; Smith *et al.*, 2008, 2011; Zielonka *et al.*, 2017). Molecules directed to mitochondria must obviously be capable of entering the cell and be at least moderately lipophilic. If mitochondrial targeting is associated with the presence of a positive charge, as is generally the case, the charge is therefore distributed by resonance over a lipophilic structure. Since the seminal study of Liberman, Skulachev and colleagues (1969), this has most often been the triphenylphosphonium group, connected to the rest of the molecule by a linker, commonly an alkyl chain. Other moderately lipophilic positively charged groups that have been used for this purpose have been mainly heteroaromatic systems, including rhodamines (e.g. Chernyak *et al.*, 2013), berberine and palmatine (Chernyak *et al.*, 2013), pyridinium (Beckham *et al.*, 2013; Hou *et al.*, 2014), indolium (Huang *et al.*, 2017) and cyanines. Constructs comprising a number of positively charged guanidinium groups have also been found to be effective mitochondria-targeting devices (Fernandez-Carneado *et al.*, 2005; Maiti *et al.*, 2007). These constructs may be considered as non-peptidic penetrating agents.

The dication dequalinium – more generally a family of compounds comprising two quinolinium moieties linked by an aliphatic chain spacer –was used early on to obtain mitochondria-targeted nanocarriers (DQAsomes), intended principally as a tool for mitochondrial transfection (e.g. Weissig, 2015). Interaction with the mitochondria was proposed to be mediated by cardiolipin (Weissig and Torchilin, 2000; Weissig *et al.*, 2001). Dequaliniums are known inhibitors of $K^+$ channels (Castle *et al.*, 1993; Galanakis *et al.*, 1996; Malik-Hall *et al.*, 2000), and – unsurprisingly at this point – they are toxic for leukaemia cells (Galeano *et al.*, 2005; Sancho *et al.*, 2007; Garcia-Perez *et al.*, 2011). Toxicity has been linked to redox unbalance (Sancho *et al.*, 2007; Garcia-Perez *et al.*, 2011). DQAsomes are at any rate only one example of the several nanostructured devices that have been devised to selectively transport cargo to mitochondria (reviewed by: Marrache *et al.*, 2015; Ma *et al.*, 2016; Paleos *et al.*, 2016; Sato *et al.*, 2016). The underlying principle generally is the use of positive charges to promote delivery to mitochondria.

To minimize the possibility of interference with the pharmacological activity, one may resort to prodrugs in which the mitochondria-targeting portion is shed, hopefully after performing its task. In some such studies, the strategy has relied on the incorporation, into the linker portion of the molecule, of a hydrolyzable bond system such as a carbamate group ( Leanza *et al.*, 2017; Peruzzo *et al.*, 2017; Teixeira *et al.*, 2017; Venturini *et al.*, 2017; Mattarei *et al.*, 2018). Insurance that the regeneration of the active principle takes place only, or mostly, at mitochondria may be a desirable feature. This may be achieved by exploiting a mitochondrial enzyme, such as nitroreductase (Chevalier *et al.*, 2016) or aldehyde dehydrogenase ALDH-2 (Ripcke *et al.*, 2009), or a reactive compound plentiful in mitochondria, such as $H_2O_2$ (McQuaker *et al.*, 2013).

The lipophilic or amphipathic character of mitochondria-targeted constructs, necessary to allow permeation of cell membranes, also confers affinity for the membranes themselves, leading to extensive binding, in particular of triphenylphosphonium (TPP)-comprising compounds (James *et al.*, 2007; Ross *et al.*, 2008). Association with membranes may pose difficulties but also be a bonus if the targeted proteins, like ion channels, reside in mitochondrial membranes. This strategy has been successfully applied recently in the case of the mitochondrial potassium channel $K_v1.3$. $MtK_v1.3$ mediates an inward potassium flux to the mitochondrial matrix and likely modulates coupling between ATP synthesis and mitochondrial respiration. *In vivo* evidence has been obtained suggesting that inhibition of $mtK_v1.3$ by pharmacological means represents an unconventional but promising strategy to selectively eliminate cancer cells. The $K_v1.3$ (and mtKv.3) channel is overexpressed in various cancer tissues/cells, and $mtK_v1.3$ was identified as a novel target of Bax (Szabo *et al.*, 2008, 2011). **Psora-4**, PAP-1 (5-(4-phenoxybutoxy)psoralen) and clofazimine, three distinct membrane-permeant inhibitors of $K_v1.3$ channels (Cahalan and Chandy, 2009), induced death in multiple human and mouse cancer cell lines by triggering a series of events involving hyperpolarization, ROS release, activation of PTP and apoptosis (Szabo and Zoratti, 2014). In contrast, membrane-impermeant, selective and high-affinity $K_v1.3$ inhibitors **ShK** or **margatoxin** did not trigger cell death, suggesting a crucial role for the mitochondrial $K_v1.3$ versus PM $K_v1.3$ channel. In preclinical mouse models for melanoma (Leanza *et al.*, 2012a) and for pancreatic ductal adenocarcinoma (PDAC) (Zaccagnino *et al.*, 2016), an i.p. injection of clofazimine significantly reduced tumour size while no adverse effects were observed in several healthy tissues. Clofazimine is a clinically used drug with anti-inflammatory and immunosuppressive activities (Cholo *et al.*, 2012). This drug also inhibits the transporter **ABCB1 (MDR1, P-glycoprotein 1)** (Van Rensburg *et al.*, 1994) and may activate the tumour suppressor p53 (Casey *et al.*, 2009; Patil, 2013). Therefore, a more specific drug, acting exclusively on the mitochondrial counterpart of $K_v1.3$, was required to more efficiently and specifically target this channel. Two mitochondriotropic derivatives of PAP-1, the most specific membrane-permeant inhibitor, were designed and synthesized and shown to drastically reduce tumour growth at a low concentration in animal models for melanoma and PDAC, without causing *in vivo* side effects such as cardiotoxicity and immune depletion (Leanza *et al.*, 2017). These mitochondria-targeted $mtK_v1.3$ inhibitors, therefore, can be considered especially promising molecules for the treatment of several types of cancer, provided the tumour cells express high levels of $mtK_v1.3$. A recent study identified some TPP-related compounds that might even eradicate cancer stem cells (Ozsvari *et al.*, 2018).

An alternative strategy to target mitochondria may still exploit transmembrane potential differences but make use of peptides rather than of lipophilic charged groups like TPP (reviewed by: Yousif *et al.*, 2009b; Frantz and Wipf, 2010; Zielonka *et al.*, 2017). This approach may be considered to be related to the use of so-called 'cell-penetrating peptides' (CPPs) to overcome the barrier posed by the plasma membrane (reviewed by: Borrelli *et al.*, 2018; Guidotti *et al.*,

2017; Kalafatovic and Giralt, 2017). CPPs are short sequences of amino acids, typically comprising basic residues along with hydrophobic ones, which are taken up by cells mostly via endocytotic pathways (clathrin- or caveolin-mediated, macropinocytosis) – entailing a subsequent escape from the endosome – or via processes involving a degree of membrane disorganization, for example, the formation of transient pores, which can result in toxicity (reviewed by: Cleal *et al.*, 2013; LeCher *et al.*, 2017; Walrant *et al.*, 2017).

Reaching the cytosol in principle allows a second-stage delivery to other subcellular compartments (Cerrato *et al.*, 2017; Ngwa *et al.*, 2017). This has been achieved in a mitochondria-specific manner with the so-called Szeto–Schiller peptides, in particular SS-31 (e.g. Szeto, 2006, 2014) (for other examples, see Cerrato *et al.*, 2017; Zielonka *et al.*, 2017). These devices, which interact with cardiolipin, have antioxidant effects. Peptides can in principle serve to transport small-molecule cargos linked via peptide bonds (Yousif *et al.*, 2009a; Jean *et al.*, 2016). A variation on the theme involves gramicidin S, a natural peptidic antibiotic with a marked affinity for mitochondrial membranes (Kanai *et al.*, 2007; Frantz and Wipf, 2010).

Mitochondrial leader peptide sequences in principle offer a specific approach, as they are recognized and accepted by the mitochondrial protein import system (MPTS), which, incidentally, needs a transmembrane potential to operate (Wiedemann and Pfanner, 2017). The attempts to deliver cargo to mitochondria in this manner have been few (Vestweber and Schatz, 1988, 1989; Flierl *et al.*, 2003), but the idea has been adapted to favour interactions of multifunctional nanocarriers with mitochondria (Kawamura *et al.*, 2013).

With regard to mitochondrial ion channels, peptides have been used to functionally modulate VDAC. The most relevant case may be that of its interaction with hexokinase, which results in inhibition of apoptosis, promotion of glycolysis and cancer cell survival (Nakashima, 1989; Zaid *et al.*, 2005; Galluzzi *et al.*, 2008; Krasnov *et al.*, 2013). The interaction was mapped to the N-terminal portion of VDAC, and detachment of hexokinase was accomplished by methyljasmonate, a plant hormone (Goldin *et al.*, 2008). More efficient are specific peptides based on the relevant sequences and made into membrane-penetrating peptide that antagonized the interaction and had pro-apoptotic effects *in vitro* (Arzoine *et al.*, 2009; Prezma *et al.*, 2013). A recent paper reports that two VDAC1 N-terminal sequences fused to a cell-penetrating sequence from the *Drosophila* antennapedia-homeodomain or to a human transferrin receptor (hTfR)-recognition sequence, respectively, were able to attack glioblastoma, a notoriously elusive target, also in an *in vivo* murine xenograft model. At least the transferrin-based construct was able to cross the blood brain barrier and was thus effective in an orthotopic model upon i.v. administration as the free compound or as an inclusion in PLGA nanoparticles (Shteinfer-Kuzmine *et al.*, 2017). The same group provided evidence that a cell-penetrating peptide derived from VDAC1 is also highly effective against hepatocellular carcinoma in a preclinical model (Pittala *et al.*, 2018).

It should also be mentioned that the pH difference between the mitochondrial matrix and cytoplasm (more alkaline in the matrix) may be exploited to drive the accumulation of permeant weak acids into mitochondria. Normally, however, this difference is in the order of only 0.5 units, permitting a concentration difference of about three. This approach therefore has not been much used, but it should be kept in mind.

## Conclusions

The field of mitochondrial ion channels can be likened to a vast stretch of territory comprising some freshly ploughed, fertile, already productive land and a dense thicket waiting to be cleared to put the ground to further good use. To do so will involve imaginative research to design specific drugs or specifically targeted drugs and to reach a more detailed understanding of their distinct localization-dependent functions, of the partnerships – with proteins and lipids – involved in the execution of these functions, of the signalling pathways affected, of the mechanisms regulating ion channel localization and of their possible modulation, of possible species and/or tissue specificities for each of these aspects. Subcellular targeting of drugs is clearly a new frontier of pharmacological science and the practical exploitation of mitochondrial channels for the improvement of public health is one of the goals the metaphorical pioneers/researchers have set for themselves. As in many other cases, the effectiveness and specificity of drug delivery is a major hurdle.

### *Nomenclature of targets and ligands*

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b,c,d,e,f).

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## Conflict of interest

The authors declare no conflicts of interest.

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