Biochimica et Biophysica Acta 1797 (2010) 132–136

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Abstracts

S16 Mitochondrial Ion Channels

Lectures

16L.1 Regulation of mitochondrial K_{ATP} channels

Uta C. Hoppe
University of Cologne, Department of Internal Medicine III, Cologne, Germany
E-mail: uta.hoppe@uni-koeln.de

Potassium (K^+) channels of the inner mitochondrial membrane influence cell function and survival. Increasing evidence indicates that multiple signaling pathways and pharmacological actions converge on mitochondrial adenosine triphosphate-sensitive K^+ (mitoK_{ATP}) channels and protein kinase C (PKC) as pivotal components of cytoprotection against necrotic and apoptotic cell injury. However, the molecular structure of mitoK_{ATP} channels remains unresolved, and no mitochondrial phosphoprotein has yet been identified that may mediate cytoprotection by these kinases. By patch-clamping the inner membrane of subsarcolemmal murine cardiac mitochondria we found that genetic connexin 43 (Cx43) deficiency, pharmacological connexin inhibition by carbenoxolone or Cx43 blockade by the mimetic peptide ^{43}GAP27 significantly reduces diazoxide-mediated stimulation of mitoK_{ATP} channels, explaining loss of cytoprotection in *Cx43*$^{+/-}$ mice *in vivo*. Suppression of mitochondrial Cx43 inhibited mitoK_{ATP} channel activation by PKC. MitoK_{ATP} channels of interfibrillar mitochondria, which do not contain any detectable Cx43, are completely drug- and PKC-insensitive, (i) confirming the fundamental role of Cx43 for mitoK_{ATP} channel stimulation, and (ii) indicating compartmentation of mitochondria in cell signaling. Our results define a novel molecular function of mitochondrial Cx43 and provide a link between cytoprotective stimuli and mitoK_{ATP} channel opening. Thus, mitochondrial Cx43 is an attractive target for drug development against cell injury.

doi:10.1016/j.bbabio.2010.04.392

16L.2 The mitochondrial apoptosis-induced channel, MAC, and Bcl-2 family proteins are co-conspirators in a deadly plot

Kathleen W. Kinnally, Shin-Young Ryu,
Pablo M. Peixoto, Laurent M. Dejean
New York University College of Dentistry, Department of Basic Sciences, New York, USA
E-mail: kck1@nyu.edu

Apoptosis is essential to mechanisms controlling tissue homeostasis and is involved in a variety of pathologies including degenerative diseases, aging, and cancer. Bcl-2 family proteins regulate this cell death program by controlling the formation of the mitochondrial apoptosis-induced channel, or MAC. Assembly of MAC corresponds to the commitment step of apoptosis, as MAC provides the pathway across the outer membrane for the release of cytochrome *c* and other pro-apoptotic factors from mitochondria [1]. While anti-apoptotic Bcl-2 antagonizes MAC activity, oligomers of the pro-apoptotic members Bax and/or Bak are essential structural component(s) of MAC [2]. In fact, assembly of MAC from Bax or Bak was monitored in real time by directly patch-clamping mitochondria with micropipettes containing the sentinel tBid, a direct activator of Bax and Bak [3] Recently, high affinity inhibitors of MAC (iMACs) were identified by Peixoto et al. [4]. Our ability to pharmacologically open and shut MAC may provide crucial clues in mechanistic studies of apoptosis and have potential therapeutic applications.

References
[1] Pavlov *et al.* (2001) *J. Cell. Biol.* **155:** 725–731.
[2] Dejean *et al.* (2005) *Mol. Biol. Cell.* **16:** 2424–2432.
[3] Martinez-Caballero *et al.* (2009) *J. Biol. Chem.* **284:** 12235–12245.
[4] Peixoto *et al.* (2009) *Biochem. J.* **423:** 381–387.

doi:10.1016/j.bbabio.2010.04.393

16L.3 Contribution of the mitochondrial potassium channel Kv1.3 to the regulation of programmed cell death

Erich Gulbins[1], Nicola Sassi[2], Heike Grassmè[1], Luigi Leanza[3], Mario Zoratti[2], Ildikò Szabò[3]
[1]*Department of Molecular Biology, University of Essen, Hufelandstrasse 5, Essen, Germany*
[2]*CNR Center for Neurosciences, viale G. Colombo 3, Padova 35122, Italy*
[3]*Department of Biology, University of Padova, viale G. Colombo 3, Padova 35122, Italy*
E-mail: ildi@civ.bio.unipd.it

Mitochondria have been shown to play a pivotal role in apoptotic signalling in various cell types. We have recently reported that in lymphocytes the voltage-gated potassium channel Kv1.3, known to reside in the plasma membrane, is active also in the inner mitochondrial membrane [1]. Upon induction of apoptosis, outer-membrane inserted Bax binds to and inhibits Kv1.3 resulting in hyperpolarization, an increase in reactive oxygen species production and cytochrome *c* release. In cells lacking Kv1.3 these events do not take place. The physiological relevance of Kv1.3 for apoptosis is illustrated by the facts that knockdown of Kv1.3 expression in human peripheral blood lymphocytes impairs apoptosis in these cells, and expression of mitochondria-targeted Kv1.3 is sufficient to sensitize to apoptotic stimuli resistant CTLL-2 T lymphocytes, which lack Kv channels [2]. Recombinant Kv1.3, when pre-incubated with Bax, prevents the actions of Bax at the level of mitochondria [3]. Data obtained with mutant Bcl-2 family proteins further point to an important role of this channel in the sequence of

0005-2728/$ – see front matter