Peer Review Report

Review Report on Understanding mitochondrial potassium channels: 33 years after discovery

Mini Review, Acta Biochim. Pol.

Reviewer: Agata Wawrzkiewicz-Jałowiecka
Submitted on: 30 Apr 2024
Article DOI: 10.3389/abp.2024.13126

EVALUATION

Q 1 **Please summarize the main theme of the mini review**

The minireview offers a summary of the significant discoveries and features of mitochondrial potassium channels drawn from research conducted by various groups over the past three decades. The Author, who is one of the international leaders in the field of research on mitoK channels, outlines both primary observations as well as key concepts regarding these channels, and discusses the ongoing studies focusing on elucidating their roles in cellular physiology and pathology. Additionally, the potential avenues for future exploration in mitochondrial potassium channel research are proposed.

Q 2 **Please highlight the limitations and strengths.**

Strengths: The submitted minireview is a concise summary of the state of knowledge about the mitochondrial potassium channels. It describes all principal features of these channels, discusses the biological implications of their activity, and indicates some new directions and challenges for the mitoK channel-oriented research. The article is short and to the point.
Limitations: the minireview form limits the length and content of the work. Reasonably, such article construction has to assume some previous experiences of the reader with the channel-oriented research, as well as their knowledge of basic concepts and terminology related to this research area. Moreover, both the number of studies mentioned and the aspects of the mitoK channels activity are subjects of restrictions imposed by the article type.

Q 3 **Does the review include a balanced, comprehensive and critical view of the research area?**

Yes. The review is generally well-written. It presents the ideas clearly and includes a short but balanced, comprehensive, and critical view of the research area. The Author turns attention both to controversies and questionable issues, that existed in the field for years, as well as the recent advances. The possible new directions and challenges for the mitoK channel-oriented research are also proposed.

Check List

Q 4 **Is the English language of sufficient quality?**

Yes.

Q 5 **Is the quality of the figure and/or table satisfactory?**

Yes.

Q 6 **Does this manuscript refer only to published data? (unpublished or original data is not allowed for this article type)**

Yes.

Q 7 **Does the manuscript cover the topic in an objective and analytical manner?**

Yes.

Q 8 **Does the reference list cover the relevant literature adequately and in an unbiased manner?**

Yes.

Q 9 **Does the manuscript include recent developments?**

Yes.

Q 10 **Does the review add new insights to the scholarly literature with respect to previously published reviews?**

Yes.

Q 11 **Please provide your detailed review report to the editor and authors (including any comments on the Q4 Check List):**

The submitted minireview offers a summary of the significant discoveries and features of mitochondrial potassium channels drawn from research conducted by various groups over the past three decades. The Author, who is one of the international leaders in the field of research on mitoK channels, outlines both primary observations as well as key concepts regarding these channels, and discusses the ongoing studies focusing on elucidating their roles in cellular physiology and pathology. Additionally, the potential directions for future exploration in mitochondrial potassium channel research are proposed.
The work is well-written and reasonably structured. The ideas are clearly presented. I am not a native speaker, but I am convinced that English language is of sufficient quality.
I have only minor remarks (Most of them are optional suggestions.):
1. In the abstract (line 17), it is written: “It is believed that K+ influx is catalyzed by various potassium channels present in the inner mitochondrial membrane. ” I agree with the Author that volume homeostasis of the mitochondrial matrix is mediated by the K+ channels. However, in the aforementioned sentence I would consider replacing the word “catalyzed” with, for example, “mediated” just to avoid the possible kinetic and thermodynamic connotations, that require from the reader to further consider the possible mechanistic picture of the channel transport of K+ ions through the mitochondrial membranes.
2. I do not see the reference to Figure 1 throughout the manuscript text. Therefore, now it is not clear where should it be located, whether is it a graphical abstract, or rather should it be placed somewhere within the Introduction. Moreover, that is a small detail, but I think that in this figure the frame with the name “INNER MEMBRANE” might be located a little lower in the top panel of the figure 1 because now it spans mainly through the outer membrane.

3. In section THE TROUBLESOME PHARMACOLOGY OF MITOCHONDRIAL POTASSIUM CHANNELS (lines 226-228) it is written, “In contrast, toxins isolated from the venom of various scorpion species such as iberiotoxin specifically (at low concentration) inhibit the activity of mitoK channels (Augustynek et al., 2017).” I think, that the specificity of the iberiotoxin might be more precisely determined; in particular, considering the large-conductance voltage- and Ca2+-activated K+ channels.
4. I am pondering the list of six fundamental observations and most important ideas dealing with mitochondrial potassium channels mentioned in the abstract and specified in the Introduction. It embraces: “1). Discovery of mitoK channels in various tissues; 2). Cytoprotection (cardioprotection, neuroprotection) induced by mitoK channels activation; 3). Cancer cell death by mitoK channels inhibition; 4). Identification of mitoK channels molecular identity; 5). Role of mitoK channels in aging/senescence/life span; 6). Interactions of mitoK channels with respiratory chain.”
I agree that all these aspects are discussed in the main body of the manuscript. Nevertheless, there is no one-to-one relation between these bullet points/ideas and the content of the 5 following sections forming the manuscript’s main body. Since I am convinced that the review is reasonably structured, I think, that for better concurrence between the list of ideas dealing with mitochondrial potassium channels and the content of the manuscript sections, this list could be slightly modified, for example:
1). Discovery of mitoK channels in various tissues and identification of their molecular identity; 2). Cytoprotection (cardioprotection, neuroprotection) induced by mitoK channels activation; 3). Cancer cell death by mitoK channels inhibition; 4). Role of mitoK channels in aging/senescence/life span; 5). Interactions of mitoK channels with respiratory chain; 6). Druggability of the mitoK channels.
5. Considering the possibility of specific modulation of the mitoK channels, this is one of the most challenging issues and the number of literature reports describing a successful specific modulation of mitoK channels is strictly limited. Nevertheless, in one of my recent works, we have found three quite interesting articles that describe the pharmacological modulation of mitochondrial potassium channels in cancer:

1). Bachmann, M., Rossa, A., Varanita, T. et al. Pharmacological targeting of the mitochondrial calcium-dependent potassium channel KCa3.1 triggers cell death and reduces tumor growth and metastasis in vivo. Cell Death Dis 13, 1055 (2022). https://doi.org/10.1038/s41419-022-05463-8 (blocking mitoK3.1 but not K3.1 with the inhibitor TRAM-34 results in the in vitro death of tumor cells and reduces their metastatic spread in vivo)

2). Bachmann, M., Rossa, A., Antoniazzi, et al. (2021). Synthesis and cellular effects of a mitochondria-targeted inhibitor of the two-pore potassium channel TASK-3. Pharmacological Research, 164, 105326. https://doi.org/10.1016/j.phrs.2020.105326 (The role of potassium channels located in the mitochondrial membrane has been highlighted by the discovery of a new inhibitor of the K29.1 (TASK-3) channel. The mitochondrial version of this inhibitor (mitoIN-THPP) was seen to decrease the survival of breast cancer cells and kill melanoma cells, whereas IN-THPP was unable to do it, highlighting the importance of potassium channels located in the mitochondrial membrane as privileged pharmacological targets in the therapy of various forms of cancer)

3). Severin, F., Urbani, A., Varanita, T. et al. Pharmacological modulation of the Kv1.3 potassium channel selectively triggers pathological B lymphocyte apoptosis in vivo in a genetic CLL model. J Exp Clin Cancer Res 41, 64 (2022). https://doi.org/10.1186/s13046-022-02249-w (in chronic lymphocytic leukemia (CLL) Kv1.3 and K3.1 channels are highly expressed both in the plasma and mitochondrial membranes, and inhibiting mitoKv1.3 with PAPTP induces in vitro death of CLL cells, while inhibition of K3.1 with TRAM-34 decreases their proliferation. The action of PAPTP was also exerted on CLL cells resistant to ibrutinib, and PAPTP also enhances the therapeutic action of Venetoclax by acting on mitoKv1.3. PAPTP also decreases CLL in vivo in animal models of CLL).

Mentioning these studies in the submitted minireview might be optionally considered by the Author.

QUALITY ASSESSMENT

Q 12 **Quality of generalization and summary**

Q 13	Significance to the field	
Q 14	Interest to a general audience	
Q 15	Quality of writing