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Mitochondrial homeostasis in cellular models of Parkinson's Disease

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Reviewer 1

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*Only major points from review and responses included.

Round 1

Reviewer 1

The field of mitochondrial dysfunction in models of PD is huge. In my opinion the manuscript needs clear inclusion criteria and an outline of the applied search strategies: otherwise the selection of these and not (similar) other studies is unclear.

Authors

We have clarified the inclusion criteria in the section 5.

Reviewer 1

Linked to point 1, primary (murine) cell models are mentioned several times: it is unclear, why no section (and analysis) has been dedicated to these approaches. If these models are not considered, at least a conclusive reason for that would be desirable (see examples in point 4).

Authors

Initially we wanted to focus on cell lines dividing in culture. However, upon reviewer's suggestion we have now included primary murine cell models in the text and data analysis for completeness.

Reviewer 1

Lines 321ff: "Despite the recognized importance of other mutations like a-synuclein and LRKK2, mitochondrial homeostasis has not been thoroughly addressed in murine models comprising their mutations." Re-check, I don't think that this argument is supportable. Some papers on mouse models that investigated genetically modified SNCA mice or pathology seeding with regard to mitochondrial functions are listed below:

- Ellis, Christopher E., et al. "Mitochondrial lipid abnormality and electron transport chain impairment in mice lacking α-synuclein." Molecular and cellular biology 25.22 (2005): 10190-10201.

- Ludtmann, Marthe HR, et al. "Monomeric alpha-synuclein exerts a physiological role on brain ATP synthase." Journal of Neuroscience 36.41 (2016): 10510-10521.

- Song, David D., et al. "Enhanced substantia nigra mitochondrial pathology in human α-synuclein transgenic mice after treatment with MPTP." Experimental neurology 186.2 (2004): 158-172.

- Burtscher, Johannes, et al. "Pronounced α-synuclein pathology in a seeding-based mouse model is not sufficient to induce mitochondrial respiration deficits in the striatum and amygdala." Eneuro 7.4 (2020).

Authors

We have included more detail on the a-synuclein models as suggested.

Reviewer 1

Also models of aSyn pathology seeding/exposure should be included in section 4 or at least it should be explained why they are not considered. Some examples:

- Wang, Xinhe, et al. "Pathogenic alpha-synuclein aggregates preferentially bind to mitochondria and affect cellular respiration." Acta neuropathologica communications 7.1 (2019): 1-14.

- Mahul-Mellier, Anne-Laure, et al. "The process of Lewy body formation, rather than simply α-synuclein fibrillization, is one of the major drivers of neurodegeneration." Proceedings of the National Academy of Sciences 117.9 (2020): 4971-4982.

- Tapias, Victor, et al. "Synthetic alpha-synuclein fibrils cause mitochondrial impairment and selective dopamine neurodegeneration in part via iNOS-mediated nitric oxide production." Cellular and Molecular Life Sciences 74.15 (2017): 2851-2874.

- Burtscher, Johannes, et al. "Pronounced α-synuclein pathology in a seeding-based mouse model is not sufficient to induce mitochondrial respiration deficits in the striatum and amygdala." Eneuro 7.4 (2020).

- Ugalde, Cathryn L., et al. "Misfolded α-synuclein causes hyperactive respiration without functional deficit in live neuroblastoma cells." Disease models & mechanisms 13.1 (2020).

Authors

We have now included the PFF model in the text and analysis.

Reviewer 1

Line 324: I would suggest to include more up to date literature on mitochondrial quality control in PD, as this important and emerging aspect is mentioned. e.g.

- Hu, Di, et al. "Alpha-synuclein suppresses mitochondrial protease ClpP to trigger mitochondrial oxidative damage and neurotoxicity." Acta neuropathologica 137.6 (2019): 939-960.

- Lautenschläger, Janin, et al. "Intramitochondrial proteostasis is directly coupled to α-synuclein and amyloid β1-42 pathologies." Journal of Biological Chemistry 295.30 (2020): 10138-10152.

Authors

We have included this suggestion. However, a full review of mitochondria quality control, molecular and organellar level is beyond the scope of this work.

Reviewer 1

Figure 1: it should be indicated in which studies SH-SY5Y were differentiated in which not. Although the comparability of differently differentiated SH-SY5Y cells will still be limited, I think it is important, because undifferentiated SH-SY5Y cells have very low basal respiration – observed changes of respiration in PD-models thus should be interpreted extra-cautiously.

Authors

We have indicated the studies including differentiated cells in the supplementary table.

Reviewer 1

Section 5: the advantages of the different models are discussed in terms of technical parameters. It would be important to also discuss the clinical relevance. PD-models have been notoriously unsuccessful to translate to patient applications. May a reason be that mitochondrial deficits are not modelled correctly? Also the previously discussed problems with medium composition and other cell culturing conditions could be taken into consideration also in this part.

Authors

This discussion has been included as suggested in the ‘Prospective’.

Round 2

Reviewer 1

The review –structurally, formally and with regard to contents – has been greatly improved. The discussion of the models appears more logical and better structured.

I hope the authors will be patient but I believe there are still some outstanding issues to increase the quality of the manuscript further. Still, several ambiguities and unclear statements currently reduce readability (and credibility) of some parts of the review and in my opinion are very important to address:

2.3: cytosol in the definition of mitochondrial membrane potential is wrong: "the difference in charge between the mitochondrial matrix and the cytosol"

Authors

We thank the reviewer for noticing this, we have made the appropriate correction in the text. - "difference in charge across the inner mitochondrial membrane"

Reviewer 1

2.4: consider to substitute « Mitochondrial Fragmentation/ Elongation » with mitochondrial dynamics and use terminology consistently and define: it is difficult to follow, if elongation and fusion or fragmentation and fission are considered as the same things and which processes are described by "dynamics" (e.g. are biogenesis, trafficking, etc included in this term?

Authors

We agree with the reviewer, and we have made the appropriate change in the text.

Reviewer 1

Line 239-242: "…triggered by the expression of an unfolded protein in the mitochondrial matrix": this sentence is very unclear – which unfolded protein? Do you mean an unfolded protein response? If so, is that beneficial or detrimental?

Authors

We appreciate the reviewer's comment, and we have clarified the text: the expression of an unfolded protein, namely deltaOTC, in the matrix in the Pink1 KO mouse accelerates neurodegeneration, thus is detrimental. Line 282

Reviewer 1

Line 258-260: "…no significant differences in OXPHOS or LEAK respiration for Complex I, Complex II or Complex III/IV" – is this sentence correct? LEAK respiration for the different complexes seems not to have been investigated in this publication.

Authors

'LEAK respiration corresponds to resting, non-phosphorylating electron transfer…', which can be achieved using oligomycin treatments. The authors of this paper use oligomycin in their experiments to achieve LEAK respiration, thus we think this is correct although the authors do not use the term 'LEAK'.

Reviewer 1

Line 420: "…higher sensitivity to oxidative stress treatments" – I assume here it means towards oxidative stress and not (therapeutic) treatment against oxidative stress; please correct to make this statement unambiguous.

Authors

We agree with the reviewer's comment, and we changed the text accordingly.

Reviewer 1

Figure 3: it should be more clearly noted in the limitations that the PD models are very different, partially explaining the different results. It would be great if the authors could discuss, on which factors the reported differences of studies reported in figure 3 depend. What may be the reasons that for some models no mitochondrial dysfunctions – or sometimes even dysfunctions in opposite directions were shown.

Authors

We have added appropriate comments for variability in results that were part of qualitative analysis and reported in Figure 3.