

Letter to the Editor

Rescue of MELAS Fibroblasts by Transfer of Wt-Mitochondria from Wharton's Jelly Mesenchyme Stem Cells May Be Ineffective in Humans

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In a recent article, Lin *et al.*, reported about the elimination of the m.3243A>G mutation burden from MELAS fibroblasts by transfer of mitochondria from Wharton's jelly mesenchymal stem cells (WJMSCs) (Lin, T.K., *et al.*,2019). The authors showed that transfer of wild-type (wt) mitochondria resulted in reduction of the mutation burden and improvement of disturbed mitochondrial functions (Lin, T.K.,*et al.*,2019). We have the following comments and concerns.

We do not agree with the conclusions that WJMSCs-based therapy is a new avenue for treating MELAS (Lin, T.K.,*et al.*,2019) . As long as this therapeutic approach has not been shown to be effective also in humans, it is premature and misleading to propagate the measure as beneficial for MELAS patients.

Furthermore, it is reported that transfer of wt-mitochondria was more effective in MF^{hi} cells as compared to MF^{neg} cells (Lin, T.K., *et al.*,2019). We should know if this was attributable to increased penetration of wt-mitochondria through more vulnerable cell membranes in MF^{hi} cells or due to decreased elimination of transferred wt-mitochondria in MF^{hi} cells.

Since the mutation load significantly declined after transfer of wt-mitochondria(Lin, T.K., *et al.*, 2019), we should know if this was due to elimination of mutated mitochondria in MF^{hi} cells or due to adding wt-mitochondria. Since both, mutation load and amount of MF^{hi} cell loss, were measured, we should be informed if

the loss of MF^{hi} cells correlated linearly with the heteroplasmy rate of the MF^{hi} cells.

Mitochondrial functions are strongly reflected by the fusion and fission kinetics of the mitochondrial network, we should be informed if also mitochondrial network dynamics improved after transfer of wt-mitochondria. It should be also demonstrated that MF^{hi} cells exhibit normal ATP production after transfer of wt-mitochondria.

It would be interesting to know if the authors also tried to transfer wt-mitochondria to MF^{neg} cells. Though MF^{neg} cells do not carry the m.3243A>G mutation per definition, it is conceivable that the mutation load was below the detection rate of the applied test, which is not mentioned in the method section. We want to know if MF^{neg} cells truly do not carry the m.3243A>G variant since it has been reported that even low heteroplasmy rates may strongly influence the random distribution of mtDNA in subsequent generations (Rong, E.,*et al.*,2018).

It should be also discussed why transfer of mitochondria only works when acceptor cells are stressed prior to transfer with the complex-I-inhibitor rotenone, LPS, or UV light. Which is the stimulus provided by recipient cells that triggers the transfer of mitochondria from WJMSCs?

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If transfer of wt-mitochondria is unlikely to be mediated via gap junctions or cell fusion, we should know how wt-mitochondria reached the target cells. The authors explain the transfer of wt-mitochondria by formation of tunneling nanotubes (TNTs). However, mitochondria are 0.5 to 10micrometers in length and may be too big to be carried by this system (Cell Biology by the Numbers).

Overall, this interesting study would profit from revising the conclusions, and from discussing a number of open questions. Before finally assessing the beneficiality of the method, application of the method in MELAS patients is a prerequisite.

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