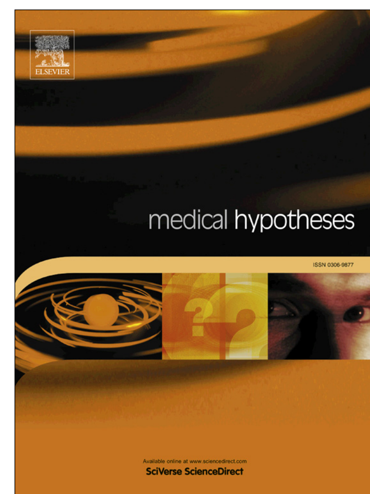
Accepted Manuscript



A synthetic mitochondrial-based vector for therapeutic purposes

Michael Renteln

PII: S0306-9877(18)30375-X
DOI: https://doi.org/10.1016/j.mehy.2018.05.014
Reference: YMEHY 8880

To appear in: *Medical Hypotheses*

Received Date: 2 April 2018
Accepted Date: 18 May 2018

Please cite this article as: M. Renteln, A synthetic mitochondrial-based vector for therapeutic purposes, *Medical Hypotheses* (2018), doi: https://doi.org/10.1016/j.mehy.2018.05.014

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

A synthetic mitochondrial-based vector for therapeutic purposes

Michael Renteln, M.S. in Molecular Genetics and Biochemistry from the University of Southern California, Ph.D. student at Baylor College of Medicine
4/18/18

Correspondence: Michael Renteln, 1757 Vistillas Rd., Altadena, CA, 91001; E-mail: mrenteln@gmail.com

Abstract
Delivery of large DNA constructs is necessary for combinatorial, anti-aging gene therapy. However, this is hindered by the lack of a non-inflammatory vector with sufficient packaging space and the ability to effectively spread through tissue. It is possible that a mitochondrion, altered to be able to secrete therapeutic proteins, could serve as an ideal gene delivery vector in this regard (for post-mitotic cells at least). Initial transfection of mitochondria with a therapeutic gene vector could be undertaken by MITO-Porter, i.e., a dual-layered fusogenic liposomal-based delivery system. Then, once a protein export pathway from the mitochondrial matrix to the cytoplasm is achieved via Sec translocon installation in the inner membrane (IM), three other components would be necessary for vector maintenance. First of all, fusion with other mitochondria must be prevented through mitofusin-cleaving protease expression on the outer membrane (OM). Second of all, mitophagy must be evaded via the expression of deubiquitylases (DUBs) on the OM. Third of all, free radical damage to the membrane over time could be prevented by shutting down electron transport chain (ETC) activity via destruction of the endogenous mitochondrial DNA (mtDNA) inside the vector – and expression of an ATP import channel to harvest sufficient energy from the host cell. The most crucial part of this plan would be to achieve Sec translocon installation in the IM. The hypothesis of this article is that Sec translocon installation into the IM may be achieved using one of a few molecular methods described herein. It is possible that it could simply occur through gene expression from a mitochondrial matrix-localized gene construct and spontaneous (or Oxa1-assisted) insertion into the mitochondrial IM. Alternatively, it could be incorporated into the MITO-Porter IM prior to fusion with patient-derived mitochondria. Lastly, it may be sent to the mitochondrial IM via the TIM/TOM complex, although hydrophobic membrane proteins may fold prematurely in the cytoplasm before reaching the mitochondrial TIM/TOM complex. Regardless, SecYEG, when present in the IM to a small degree initially, should suffice to install more copies of itself from a mitochondrial matrix-localized gene vector. After proteins (with a C-terminal tag and autotransporter domain) have been sent to the intermembrane space from the matrix in unfolded form, the endogenous SAM complex would suffice to export them to the OM, where the relevant (passenger) domain may be cleaved off by an orthogonal protease and released into the cytoplasm.

ACCEPTED MANUSCRIPT

Download English Version:

https://daneshyari.com/en/article/8515390

Download Persian Version:

https://daneshyari.com/article/8515390

Daneshyari.com