Allogeneic/xenogeneic transplantation of peptide-labeled mitochondria in Parkinson's disease: restoration of mitochondria functions and attenuation of 6-hydroxydopamine–induced neurotoxicity

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Although restoration of mitochondrial function in mitochondrial diseases through peptide-mediated allogeneic mitochondrial delivery (PMD) has been demonstrated in vitro, the in vivo therapeutic efficacy of PMD in Parkinson's disease (PD) has yet to be determined. In this study, we compared the functionality of mitochondrial transfer with or without Pep-1 conjugation in neurotoxin (6-hydroxydopamine, 6-OHDA)-induced PC12 cells and PD rat models. We injected mitochondria into the medial forebrain bundle (MFB) of the PD rats after subjecting the nigrostriatal pathway to a unilateral 6-OHDA lesion for 21 days, and we verified the effectiveness of the mitochondrial graft in enhancing mitochondrial function in the soma of the substantia nigra (SN) neuron through mitochondrial transport dynamics in the nigrostriatal circuit. The result demonstrated that only PMD with allogeneic and xenogeneic sources significantly sustained mitochondrial function to resist the neurotoxin-induced oxidative stress and apoptotic death in the rat PC12 cells. The remaining cells exhibited a greater capability of neurite outgrowth. Furthermore, allogeneic and xenogeneic transplantation of peptide-labeled mitochondria after 3 months improved the locomotive activity in the PD rats. This increase was accompanied by a marked decrease in dopaminergic neuron loss in the substantia nigra pars compacta (SNc) and consistent enhancement of tyrosine hydroxylase–positive immunoreaction of dopaminergic neurons in the SNc and striatum. We also observed that in the SN dopaminergic neuron in the treated PD rats, mitochondrial complex I protein and mitochondrial dynamics were restored, thus ameliorating the oxidative DNA damage. Moreover, we determined signal translocation of graft allogeneic mitochondria from the MFB to the calbindin-positive SN

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Submitted for publication October 5, 2015; revision submitted December 3, 2015; accepted for publication December 3, 2015.

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1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.12.003

neuron, which demonstrated the regulatory role of mitochondrial transport in alleviating 6-OHDA–induced degeneration of dopaminergic neurons. (Translational Research 2016;170:40–56)

Abbreviations: MFB = medial forebrain bundle; Mito = allogeneic mitochondria; 6-OHDA = 6-hydroxydopamine; PD = Parkinson's disease; PMD = peptide-mediated delivery of allogeneic mitochondria; SN = substantia nigra; SNc = substantia nigra pars compacta; ST = striatum; TH = tyrosine hydroxylase; xPMD = peptide-mediated delivery of xenogeneic mitochondria

AT A GLANCE COMMENTARY

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Background

Clinical application of mitochondrial transplantation could be limited because of the variable factors dependent on host property and cell environment. Previously, we have demonstrated that active delivery of mitochondrial organelle via modification with a Pep-1 carrier restored the mitochondrial function in mitochondrial disease model of myoclonic epilepsy with ragged red fiber but unknown in in vivo therapeutic remind. This study further confirmed a useful approach of Pep-1–mediated mitochondrial transplantation in Parkinson's disease via regulation mitochondrial dynamics.

Translational Significance

This study contributes to carry on the clinical practice of mitochondrial transplantation in rescue of cell damage induced by oxidative-induced stress or mitochondrial dysfunction.

INTRODUCTION

Parkinson's disease (PD) is a prevalent and disabling neurodegenerative disease involving progressive motor dysfunction, which is caused by selective degeneration of the nigrostriatal pathway. Although the specific cause of PD remains unclear, strong evidence shows that the possible underlying mechanisms of this disease are mitochondrial dysfunction, oxidative stress, defective proteolysis, and protein misfolding and accumulation.[1] In addition to maintaining energy metabolism, mammalian mitochondria govern the redox signaling implicating cell apoptosis to induce oxidative damage in numerous pathologies.[2,3] Mitochondrial dysfunction is manifested by reduced bioenergetic capacity as well as increased oxidative stress and susceptibility of neurons to excitotoxic death. Several studies have observed mitochondrial dysfunction in PD models.[4,5] Hence, emerging mitochondria-targeting therapies aimed at alleviating the severity and progression of PD[6,7] have been assessed. Such therapies include using mitochondrial bioenergetic agents,[8] mitochondria-targeted antioxidants and peptides,[6,9] the sirtuin 1 (SIRT1) activator resveratrol,[10] and the pan-peroxisome proliferator-activated receptors (pan-PPAR) agonist bezafibrate.[11] However, these therapies alleviate only the pain engendered by unhealthy mitochondria; they cannot essentially cure mitochondrial dysfunction.

Currently, a new strategic concept for supporting the regeneration of cells that incur external stress involves the activation of intercellular organelle transfer.[12] Cell rejuvenation against oxidative stress has been confirmed through the transplantation of cellular components such as mitochondrial organelle.[12,13] The mitochondria are dynamic organelle, and mitochondrial homeostasis is maintained through continuous mitochondrial fusion and fission processes.[14] Several studies have indicated that infusing or transplanting fresh isolated allogeneic mitochondria produced substantially strong protective effects against ischemia-induced injury in the heart[15] and liver.[16] In addition, in vitro transplantation of xenogeneic mitochondria derived from a murine can restore the mitochondrial respiration of human mitochondrial DNA (mtDNA)-depleted ρ° cells.[17] To date, an effective mitochondrial transplantation therapy for PD has yet to be determined; nonetheless, perturbations of mitochondrial dynamics were reported to cause a progressive retrograde degeneration of nigrostriatal dopamine neurons in mitochondrial homeostasis,[18] and loss of mitofusin 2 (MFN2) protein was determined to cause prominent mitochondrial transport defects in nigral neurons.[19]

Studies on mitochondrial transplantation have raised more questions than they have answered, and this is primarily because of the unclear mechanisms and variable factors they have presented. For example, the question as to whether functional recovery is affected by the use of dissimilar mitochondrial internalization machinery, uptake amount, or interaction of foreign and innate mitochondria in host cells has yet to be clearly resolved. In