

Mitochondrial Calcium-Triggered Oxidative Stress and Developmental Defects in Dopaminergic Neurons Differentiated from Deciduous Teeth-Derived Dental Pulp Stem Cells with MFF Insufficiency

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論 文 名	Mitochondrial Calcium-Triggered Oxidative Stress and Developmental Defects in Dopaminergic Neurons Differentiated from Deciduous Teeth-Derived Dental Pulp Stem Cells with MFF Insufficiency (MFF 機能不全のヒト乳歯由来幹細胞から分化したドーパミン作動性ニューロンにおけるミトコンドリアのカルシウム誘発性酸化ストレスと発達障害)			
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論 文 審 査 の 結 果 の 要 旨

Mitochondrial fission factor (MFF) is an adapter that targets dynamin-related protein 1 from the cytosol to the mitochondria for fission. Loss-of-function MFF mutations cause encephalopathy due to defective mitochondrial and peroxisomal fission 2 (EMPF2). To elucidate the molecular mechanisms that were involved, the authors analyzed the functional effects of MFF depletion in deciduous teeth-derived dental pulp stem cells differentiating into dopaminergic neurons (DNs). When treated with MFF-targeting small interfering RNA, DNs showed impaired neurite outgrowth and reduced mitochondrial signals in neurites harboring elongated mitochondria. MFF silencing also caused mitochondrial Ca^{2+} accumulation through accelerated Ca^{2+} influx from the endoplasmic reticulum (ER) via the inositol 1,4,5-trisphosphate receptor. Mitochondrial Ca^{2+} overload led DNs to produce excessive reactive oxygen species (ROS), and downregulated peroxisome proliferator-activated receptor- γ co-activator-1 α (PGC-1 α). MFF was co-immunoprecipitated with voltage-dependent anion channel 1, an essential component of the ER-mitochondrial Ca^{2+} transport system. Folic acid supplementation normalized ROS levels, PGC-1 α mediated mitochondrial biogenesis, and neurite outgrowth in MFF depleted DNs, without affecting their mitochondrial morphology or Ca^{2+} levels. They proposed that MFF negatively regulates the mitochondrial Ca^{2+} influx from the ER. MFF-insufficiency recapitulated the EMPF2 neuropathology with increased oxidative stress and suppressed mitochondrial biogenesis. These observations suggest that ROS and mitochondrial biogenesis might be potential therapeutic targets for EMPF2.

Based on this research, the candidate deserves to be conferred the degree of DOCTOR OF PHILOSOPHY (Dental Science) in the Graduate School of Dentistry, Kyushu University.