

MITOCHONDRIAL METABOLIC REMODELING UPON DEFECTS IN TETRAHYDROBIOPTERIN

Hyoung Kyu Kim¹, Juhyun Jeon³, Won Sun Park¹, Seung Hee Ha¹, Seong Woo Choi¹, Nari Kim¹, Yang Jae Sung³, Sanguk Kim³, Young Shik Park² and Jin Han¹

¹National Research Laboratory for Mitochondrial Signaling, Department of Physiology, Cardiovascular and Metabolic Disease Center, Medical Research Center, FIRST mitochondrial Research Group, Inje University, Busan, South Korea; ²School of Biotechnology and Biomedical Science, Inje University, Kimhae, South Korea; ³School of Interdisciplinary Bioscience and Bioengineering, Pohang University of Science and Technology (POSTECH), Pohang 790-784, South Korea.

Tetrahydrobiopterin (BH₄) is an endogenous essential cofactor for NO synthesis and metabolisms of phenylalanine, tyrosine and tryptophan. To gain a better understanding of how BH₄ orchestrate the biological processes in mitochondria and control phenotypic characteristics of an organism, we investigated the BH₄ deficiency effect on cardiac mitochondria function and proteomic alteration in sepiapterin reductase gene knock out mouse (Spr^{-/-}) which has severe BH₄ deficiency. Spr^{-/-} mouse was shown typical growth retardation induced by BH₄ deficiency compared to wild type control mouse. The cardiac mitochondrial morphology alterations in both size and number were observed under electron microscopy. As a systemic approach to evaluate global proteomic modifications in cardiac mitochondria from BH₄ deficiency model, we performed 2DE and LC-MS/MS proteomic analysis. We then performed data integrative analysis to systematically validate and organize them into significantly altered biological pathways. Our results suggested that altered proteins in BH₄ deficiency induced mitochondrial dysfunction by affecting two major key factors in mitochondria metabolism, the TCA cycle and Electron transport chain. The systemic prediction was evaluated with various functional validations. The decrease of mitochondrial nitric oxide (mtNO) and increase of ROS production in Spr^{-/-} mouse which induced oxidative damage on mitochondrial function accompanied with mitochondrial membrane potential ($\Delta\Psi_m$) depolarization, mitochondria respiration rate inhibition and mitochondrial DNA fragmentation. These findings suggested new insight of BH₄ as a novel regulator of mitochondrial function.

Key Word:

Tetrahydrobiopterin, Sepiapterin Reductase deficiency, mitochondrial dysfunction, 2DE proteomics, LC-MS/MS, pathway remodeling.