氏　　名	Liang Sha
学位の種類	博士（　人間生物学　）
学位記番号	博甲第　8307　号
学位授与年月	平成　29 年　3 月　24 日
学位授与の要件	学位規則　第４条第１項該当（昭和２８年４月１日文部省令第９号）
審査組織	グローバル教育院
学位論文題目	Mitochondrial Function and Homeostasis Regulated by Asymmetric Arginine Dimethylation (非対称型アルギニンジメチル化によるミトコンドリアの機能制御)

	（職名）	（学位）	（氏名）
主　　査	筑波大学教授	医学博士	高橋　智
副　　査	筑波大学助教	博士（理学）	水野　智亮
副　　査	筑波大学助教	博士（理学）	山下　年晴
副　　査	筑波大学教授（グローバル教育院）	Ph.D.	Margarete Heck

論文の要旨
Abstract of thesis

Protein Arginine Methyltransferase 1 (PRMT1) catalyzes asymmetric arginine dimethylation on cellular proteins and modulates various aspects of cellular processes, such as signal transduction, DNA repair, and transcriptional regulation. Prmt-1 was previously reported that pan anti-ageing factor in C. elegans and accumulating evidence has shown that it is involved in a broad spectrum of ageing-related diseases, such as myocardial infarction and hypomyelination-induced neurodegenerative diseases. However, the physiological and pathological roles of PRMT-1 remain largely unclear because of the lack of in vivo investigation. In this paper, the applicant employed C. elegans as a model organism to explore the physiological functions of PRMT-1 at whole-organism level. The applicant identified nine *in vivo* substrates of PRMT-1 by two-dimensional Western blot-based proteomic analysis using C. elegans. The subcellular localizations of these substrates spanned from extracellular matrix, cytoplasm, nucleus, to organelles such as endoplasmic reticulum and mitochondria. Because the direct relation between PRMT-1 and mitochondrial functions has never been reported, the applicant focused on the function of PRMT-1 in mitochondria. Subcellular fractionation followed by LC-MS/MS analysis showed that PRMT-1 is almost entirely responsible for asymmetric arginine dimethylation on mitochondrial proteins. Metabolome analysis showed a global

suppression of metabolism in prmt-1 deletion mutant worms, however, the mitochondrial biogenesis was not seemed to be altered. Importantly, isolated mitochondria from prmt-1-null mutants represented compromised ATP synthesis probably due to decreased activity of oxidative phosphorylation in vitro. Transgenic rescue experiments demonstrated that PRMT-1-dependent asymmetric arginine dimethylation is required to prevent mitochondrial ROS production in C. elegans. Furthermore, prmt-1-null mutation caused induction of stress response genes involving xenobiotic-detoxification and innate immune defense, as well as the metabolic process and mitochondrial genes. Direct evidence for the mitochondrial stress was observed with the activation of mitochondrial unfolded protein response. As the behavioral response, prmt-1 mutant worms exhibited food-avoidance behavior due to mitochondrial dysfunction.

審査の要旨
Abstract of assessment result

【批評 Review】

The applicant identified a novel role of PRMT-1 which facilitates the energy metabolism and also maintains the homeostasis of mitochondria by directly targeting mitochondrial proteins. These findings are expected to provide clues for understanding the physiological roles of PRMT-1 in higher organisms and add new layer of complexity to posttranslational regulation of mitochondrial function, ultimately contributing to the mechanistic or therapeutic research of mitochondria-related disorders, including cardiovascular and neurodegenerative diseases.

【最終試験の結果 Result】

The final examination committee conducted a meeting as a final examination on 3rd February, 2017. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

【結論 Conclusion】

Therefore, the final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Human Biology.