研究のタイトル

研究の内容は、脳の発達過程におけるアルギニンメチル化酵素の機能解析を目的としています。研究者は、脳の発達に重要な役割を果たす蛋白質メチル化酵素であるPRMT1を対象に、その機能解析を行いました。研究結果は、PRMT1が脳の発達に重要な役割を果たすことを示すものでした。
**Purpose**

Protein arginine methyltransferase 1 (PRMT1) is involved in cell proliferation, DNA damage response, and transcriptional regulation. While PRMT1 is extensively expressed in the central nervous system (CNS) at embryonic and perinatal stages, the physiological role of PRMT1 was poorly understood. The aim of my study was to characterize the primary function of PRMT1 during CNS development.

**Materials and methods**

CNS-specific PRMT1 knockout mice were generated by crossing PRMT1-flox mice and Nestin-Cre transgenic mice. The overall CNS development and oligodendrocyte lineage defects were tested by combining histological and behavioral analyses of the post-natal mice. Primary oligodendrocyte precursor cells (OPCs) were utilized to examine the cell intrinsic effect of PRMT1 on cell differentiation.

**Result**

CNS-specific PRMT1 knockout mice exhibited post-natal growth retardation with tremors and most of them died in two weeks after birth. Brain histological analyses revealed the prominent cell reduction in the white matter tracts of the mutant mice. Furthermore, ultrastructural analysis demonstrated that
myelin sheath was almost completely ablated in the CNS of these animals. In agreement with hypomyelination, I also observed that most major myelin proteins including MBP, CNPase, and MAG were dramatically decreased, although neuronal and astrocytic markers were preserved in the brain of CNS-specific PRMT1 knockout mice. These animals had reduced number of OLIG2+ oligodendrocyte lineage cells in the white matter. I found that expression of transcription factors essential for oligodendrocyte specification and subsequent maturation were significantly suppressed in the brain of the mutant mice. In oligodendrocyte lineage cells, PRMT1 expression was confirmed in both brains and cultured cells. In addition, PRMT1 showed stronger expression in OPCs and it gradually decreased as they differentiate. Overexpression of PRMT1 to in vitro OPCs did not affect cell differentiation rate.

Discussion

The present in vivo study provided evidence that PRMT1 is required for CNS development, especially for oligodendrocyte maturation processes. In combination with in vitro PRMT1 expression studies, it is suggested that PRMT1 is more important in immature stage of oligodendroglial differentiation. This is the first demonstration of tissue-specific PRMT1 ablation after the previous report on early-embryonic lethality of conventional PRMT1 knockout mice by an American group in 2000. In the future, identification of responsible PRMT1 targets in the CNS would surely help to know how it regulates oligodendrocyte cell development and our mutant mice might serve as a genetic model to study the possible intervention of with human hypomyelination diseases such as periventricular white matter injuries.