学位の種類	博士（医学）
報告番号	甲第１５２５号
学位記番号	第１０９６号
氏名	三崎　紀展
授与年月日	平成 28 年 3 月 25 日
学位論文の題名	The Replication Foci Targeting Sequence (RFTS) of DNMT1 functions as a potent histone H3 biding domain regulated by autoinhibition（DNMT1 の RFTS 領域はヒストン H3 結合能を有し、その機能は分子内結合により抑制される） Biochemical and Biophysical Research Communications (accept for publication)
論文審査担当者	主査：　近藤 豊 副査：　岡本 尚，中西 真

Abstract

DNA methylation plays a crucial role in the regulation of numerous biological processes, including genomic imprinting, X chromosome inactivation, and retrotransposon silencing, and also contributes to tissue-specific gene expression. DNA methyltransferase 1 (DNMT1) plays an essential role in propagation of the DNA methylation pattern to daughter cells. The replication foci targeting sequence (RFTS) of DNMT1 is required for the recruitment of DNMT1 to DNA methylation sites through direct binding to ubiquitylated histone H3 mediated by UHRF1 (Ubiquitin-like containing PHD and RING finger domains 1). Recently, it has been reported that the RFTS plugs the catalytic pocket of DNMT1 in an intermediated manner and inhibits its DNA methyltransferase activity. However, it is unclear whether this binding affects RFTS function in terms of recruitment to DNA methylation sites. Using *Xenopus* egg extracts, we demonstrate here that abrogation of the interaction between the RFTS and the catalytic center of DNMT1, by deletion of the C-terminal portion or disruption of the hydrogen bond, results in non-ubiquitylated histone H3 binding and abnormal accumulation of DNMT1 on the chromatin. Interestingly, DNMT1 mutants identified in patients with a neurodegenerative disease, ADCA-DN, bound to non-ubiquitylated histone H3 and accumulated on chromatin during S phase in *Xenopus* egg extracts. These results suggest that the interaction between the RFTS and the catalytic center of DNMT1 serves as an autoinhibitory mechanism for suppressing the histone H3 binding of DNMT1 and ensuring the accurate recruitment of DNMT1 to sites of DNA methylation. The autoinhibitory mechanism may play an important role in the regulation of gene expression in neurogenesis.