Healthcare, Drug discovery

Molecular mechanism of genome stability in postnatal brain development

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Abstract

Genome stability is essential for brain development and function, as de novo mutations during neuronal development cause psychiatric disorders. However, the contribution of DNA repair to genome stability in postnatal neurons remains elusive. Here, we demonstrate that DNA repair protein DNA polymerase β (Polβ) is involved in hippocampal pyramidal neuron differentiation via a TET-mediated active DNA demethylation during early postnatal stages using conditional knockout mice. Polβ deficiency induced extensive DNA double-strand breaks (DSBs) in hippocampal pyramidal neurons. Inhibition of DNA demethylation by suppressing TET expression diminished DSB formation. Conversely, its induction by TET1 catalytic domain overexpression increased DSBs in neurons. Furthermore, the damaged hippocampal neurons exhibited aberrant neuronal gene expression profiles and dendrite formation. Comprehensive behavioral analyses revealed impaired spatial memory and anxiety behavior in adulthood. Thus, Polβ maintains genome stability in the active DNA demethylation that occurs during early postnatal neuronal development, thereby contributing to differentiation and subsequent learning and memory.

Background & Results

Genome stability is essential for brain development and function, as de novo mutations during neuronal development cause psychiatric disorders such as autism spectrum disorders. Polβ is a core component of the base excision repair pathway, and also plays a role in the active DNA demethylation process as an epigenetic regulation. Studies using conventional Polβ-deficient mice show increased neuronal apoptosis during the period of neurogenesis in the developing nervous system rather than in other tissues, and the mice die just after birth. Further, our previous study focusing on spatiotemporal roles using forebrain-specific conditional KO mice indicates that Polβ deficiency in neural progenitors rather than in postmitotic neurons specifically leads to an increase of DNA double-strand breaks (DSBs) and apoptosis in the embryonic neocortex (Onishi et al., 2017). However, the contribution of DNA repair to genome stability in postnatal neurons remains elusive. Here, we demonstrate that Polβ is involved in hippocampal pyramidal neuron differentiation via a TET-mediated active DNA demethylation during early postnatal stages using conditional knockout mice, in which forebrain postmitotic excitatory neurons lack Polβ expression. Polβ deficiency induced extensive DSBs in hippocampal pyramidal neurons, and to a lesser extent in neocortical neurons, during a period in which decreased levels of 5-methylcytosine were observed in genomic DNA. Inhibition of the hydroxylation of 5-methylcytosine by expression of microRNAs miR-29a/b-1 diminished DSB formation. Conversely, its induction by TET1 catalytic domain overexpression increased DSBs in neocortical neurons. Furthermore, the damaged hippocampal neurons exhibited aberrant neuronal gene expression profiles and dendrite formation, but not apoptosis. Comprehensive behavioral analyses revealed impaired spatial reference memory, contextual fear memory and anxiety behavior in adulthood.

Significance of the research and Future perspective

Polβ maintains genome stability in the active DNA demethylation that occurs during early postnatal neuronal development, thereby contributing to differentiation and subsequent learning and memory in adult. It is expected to lead to understanding of the mechanism of mutagenesis that causes neuropsychiatric disorders and to the development of preventive medical methods.

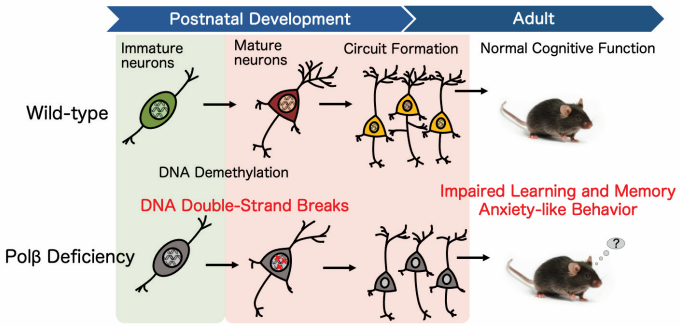

Fig. 1 Polβ deficiency influences postnatal neuronal differentiation and subsequent learning and memory in adulthood.

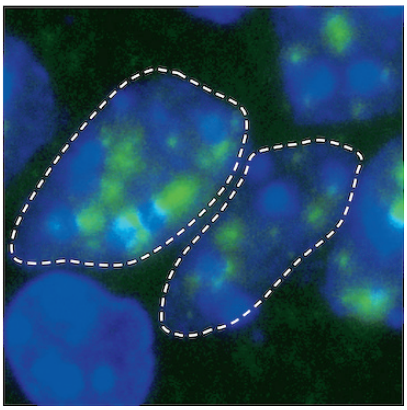

Fig. 2 Increased DNA double-strand breaks in Polβ-deficient hippocampal neurons.

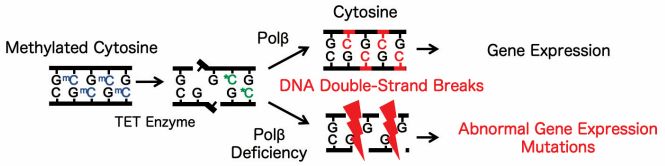

Fig. 3 Polβ contributes to active DNA demethylation that occurs during early postnatal neuronal differentiation.

Patent	
Treatise	Uyeda, A; Onishi, K; Hirayama, T et al. Suppression of DNA Double-Strand Break Formation by DNA Polymerase β in Active DNA Demethylation is Required for Development of Hippocampal Pyramidal Neurons. J Neurosci. 2020; 40: 9102-9027. doi: 10.1523/JNEUROSCI.0319-20.2020 Onishi, K; Uyeda, A; Shida, M et al. Genome Stability by DNA polymerase β in Neural Progenitors Contributes to Neuronal Differentiation in Cortical Development. J Neurosci. 2017; 37: 8444-8458. doi: 10.1523/JNEUROSCI.0665-17.2017
URL	https://www.fbs.osaka-u.ac.jp/ja/research_results/papers/detail/1008
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