

論文の内容の要旨

論文題目 Dynamic changes of epigenome and retrotransposon profiles by antipsychotics treatment and maternal immune activation

(抗精神病薬投与および母体免疫活性によるエピゲノム・レトロトランスポゾン動態の解析)

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Schizophrenia is a major psychiatric disorder that affects approximately 1 % of the population, but its pathophysiology is largely unknown. There are accumulating evidences showing that epigenetic profiles (e.g. DNA methylation) are involved in the pathophysiology of neuropsychiatric disorders and mechanisms of action of antipsychotics. In this thesis, I investigated for the epigenetic mechanisms of an antipsychotic drug using a cellular model, and examined the epigenetic status of the fetal brain of an animal model of schizophrenia by focusing on long interspersed element (LINE)-1 retrotransposon, which showed increased copy number in schizophrenia previously.

In the first part of my study, I performed a comprehensive DNA methylation analysis in human neuroblastoma cells treated with blonanserin, an antipsychotics, using a beadarray. Administration with blonanserin resulted in dose-dependent changes in DNA methylation at genomic regions related to axonogenesis and neuron differentiation, suggesting the epigenetic mechanisms as the possible pharmaceutical targets of the antipsychotics.

I then examined the epigenetic status of fetal brain of poly(I:C) mouse model, a maternal immune activation model of psychiatric disorders. I showed that LINE-1 copy number was stably increased after repeated injection of a low poly(I:C) dose. Transcriptome and proteome analyses by RNA sequencing and iTRAQ revealed the activation of host defense mechanisms in embryonic neural stem/progenitor cells after poly(I:C) exposure. Epigenetic analyses revealed the increased LINE-1 hydroxymethylation level, suggesting that the epigenetic mechanisms may underlie increased LINE-1 activity in the brain of poly(I:C) model. The present epigenetic studies provided new insights into pharmaceutical targets and possible mechanisms of the pathophysiology of schizophrenia.