Evaluation of Testicular Toxicity By Sperm Epigenetic Status

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Kazuya SAKAI, Kenshiro HARA and Kentaro TANEMURA

Graduate School of Agricultural Science, Tohoku University

Testicular toxicity is a frequent adverse effect of the surrounding environment such as temperature, radiation, and environmental chemicals. However, there is no effective biomarker to detect testicular toxicity noninvasively. To find new biomarkers, we focused on epigenetic factors in the male germline. In this study, we investigated changes to sperm DNA methylation and sperm RNA profiles in mouse models of testicular toxicity induced by doxorubicin (DXR). We established mouse models of early-stage testicular toxicity and testicular pre-toxicity by the administration of 0.2 mg/kg and 0.02 mg/kg DXR, respectively, twice weekly for 5 weeks. Histological analysis showed sparse abnormalities in testicular tissue; however, western blotting analysis revealed reduced testicular expression levels of DNA methyltransferases Dnmt3a and Dnmt3b in both DXR-treated groups. Interestingly, comprehensive sperm DNA methylation analysis using Methyl-CpG binding domain protein-enriched genome sequencing (MBD-seq) revealed that hypomethylation was the most frequent change induced by DXR. Moreover, in sperm RNA-seq analysis, we found that some differences in RNA contents between DXR-treated and untreated groups. These findings suggest that sperm epigenetic factors may be used as an early diagnostic marker for testicular changes not detected by conventional toxicity analysis.