学位の種類	博士（医学）
報告番号	甲第１４０４号
学位記番号	第１００９号
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授与年月日	平成 26 年 3 月 25 日
学位論文の題名	Distinctive Changes in Histone H3K4 Modification Mediated via Kdm5a Expression in Spermatogonial Stem Cells of Cryptorchid Testes （停留精巣の精子幹細胞における Kdm5a 発現を介した特異的なヒストン H3K4 修飾の変化） Journal of Urology, in press
論文審査担当者	主査：　中西 真 副査：　高橋 智，郡 健二郎

Abstract

Purpose: Spermatogenesis involves a series of tightly controlled genetic events in germ cells ranging from spermatogonia to spermatozoa. Gonocytes differentiate into spermatogonial stem cells (SSCs), which make it possible to maintain spermatogenesis continuously throughout life. Previously, we reported attenuation of SSC activity in cryptorchid testes, which resulted in altered spermatogenesis and affected fertility. However, few studies have examined the differentiation process from gonocytes to SSCs. To clarify the underlying mechanisms comprehensively, we performed microarray analyses to assess differential expression of transcripts between normal and undescended testes (UDT) in juvenile rats.

Materials and Methods: Using microarray analysis, we compared whole mRNA expression of normal and cryptorchid testes in a rat model. Subsequently, we validated the differential expression of candidate genes by real-time RT-PCR, and performed immunohistochemistry. Furthermore, we investigated the methylation status of histone H3K4 in the cryptorchid testes and GC-1 spermatogonial cell line.

Results: Twenty-four upregulated and 39 downregulated genes were detected. Among these genes, *Kdm5a* expression was significantly higher in UDT. Immunohistochemistry showed that Kdm5a was localized in the nuclei of gonocytes, spermatogonia, and spermatocytes. Expression levels of H3K4me3/me2 were decreased in UDT at 9 dpp. Furthermore, overexpression of

Kdm5a in GC-1 cells led to increased expression of *Esr2*, *Neurog3*, *Pou5f1*, *Ret*, and *Thy1*.

Conclusions: Recent investigations revealed that not only genetic but also epigenetic regulation plays a role in spermatogenesis. It is likely that Kdm5a is involved in the process of transformation of gonocytes into SSCs by means of transcriptional regulation of specific genes, via H3K4 histone modification. This is the first report of epigenetic analyses of germ cell differentiation during early spermatogenesis.