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ABSTRACT

Purpose: To elucidate the mechanism of spermatogonial stem cell (SSC) disturbance of cryptorchidism, we investigated expression of microRNAs (miRNAs) and their target genes in undescended testes.

Materials and Methods: Using microarray analysis, we compared total miRNA expression in unilateral undescended testes (UDT) with that of contralateral descended testes (DT) and normal testes in a rat model of cryptorchidism, which is derived by administering flutamide to pregnant Sprague-Dawley rats. We identified mRNA targets of miRNAs by bioinformatic analysis, followed by *in situ* hybridization and immunohistochemistry to localize the candidate miRNAs and mRNAs, respectively. We also investigated whether miRNAs could inhibit target protein expression in vitro.

Results: Microarray analysis and following qPCR showed that only miR-135a was expressed at a lower level in UDT, and we identified its target as *FoxO1*, which is essential for stem cell maintenance. miR-135a and FoxO1 localized to SSCs, and moreover, FoxO1 localized to the SSC nucleus less frequently in UDT, indicating that the activity of FoxO1, which acts as a transcription factor, is altered in UDT. Finally, transfection of miR-135a into spermatogonia in vitro resulted in

downregulation of FoxO1 expression.

Conclusions: In cryptorchid testes there are reduced numbers of SSCs in which FoxO1 is activated, indicating that a failure of SSC maintenance results in alteration in spermatogenesis. We also reveal the interaction between miR-135a and FoxO1, and finally propose that miR-135a contributes to spermatogonial stem cell maintenance through modulation of FoxO1 activity.