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# miR22-5p targets TET2 and regulates the Estrogen receptor 2 expression in infertile women with mild or minimal endometriosis during implantation window

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Context: Our previous microRNA (miR) microarray data in mid-luteal endometrium of minimal or mild endometriosis showed a decreased expression of miR22-5p. The Ten-Eleven Translocation 2 (TET2) plays an important role in DNA demethylation. The endometrial receptivity and progesterone resistance in minimal or mild endometriosis during implantation window, which was identified without substantial pelvic anatomical changes.

Objective: To determine the role of miR22-5p in the pathogenesis of mild endometriosis associated with infertility.

Patients, Methods, and Main Outcome Measures: Normal endometrium was obtained from 24 disease-free women, eutopic endometrium was obtained from 26 women with a laparoscopic and histological diagnosis of stage I–II endometrios. miR22-5p expression was analyzed in the mid-luteal endometrium with or without minimal or mild endometriosis. Bioinformatics analysis predicted that miR22-5p targeted TET2 3-untranslated region. TET2 expression was analyzed by quantitative RT-PCR, Western Blot and immunohistochemistry. 5-hmC levels were determined by Dot blot and immunofluorescence staining. ESR2 was measured by qRT-PCR and Western Blot, its promoter methylation detected by Bisulfite Modification and Sequencing analysis.

Results: miRNA22-5p was differentially downregulated in eutopic endometrium of minimal or mild endometriosis. TET2 expression was significantly inhibited by miR22-5p overexpression in eutopic endometrial stromal cells (ESCs) and upregulated by miR22-5p inhibition in normal ESCs directly. ESR2 was also significantly regulated by miR22-5p, Bisulfite sequencing of ESR2 promoter region (-197/+359) showed no significantly changes of promoter region methylation by miR-22-5p transfection.

Conclusions: We demonstrated firstly that miR22-5p expression was decreased in minimal or mild endometriosis during implantation window. TET2 was a key directly target of miR22-5p, the overexpression of TET2 of endometrium in minimal or mild endometriosis during implantation window may contribute to its associated infertility. MiR22-5p regulated the expression of ESR2, but do not directly affect the methylation of ESR2 promoter region. This study provides a novel approach for the imbalance of miR-22-5p expression in mid-luteal endometrium of minimal or mild endometriosis, may contribute to the mechanism of its associated infertility.

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