News Release

Title

Novel ovarian endometriosis model causes infertility via iron-mediated oxidative stress in mice

Key Points

- **Newly established mouse model of ovarian endometriosis**
- **Iron-mediated oxidative stress induced infertility in mouse**
- **This model would contribute to further research on endometriosis-related infertility and ovarian cancer.**

Summary

We established a novel mouse model of ovarian endometriosis and evaluated iron-mediated oxidative stress-induced infertility in our model.

Various mouse models of endometriosis, such as peritoneal or deep endometriosis mouse model, have been developed. However, the mouse model of ovarian endometriosis inducing follicular dysfunction and infertility has not been reported. Thus, we established a new mouse model of ovarian endometriosis which is available to evaluate oxidative stress on ovarian follicles and infertility. *C57BL/6N* female mice (9-week old) were enrolled in this study and devided into 3 groups; Control (C), Sham operation (S) and Ovarian endometriosis (OE). The donor uterine fragments were implanted on the ovary surface of recipient mouse. Then, they were euthanized 1, 2 and 4 weeks after surgery for histological evaluation of the development of endometriosis, fibrosis, iron accumulation. Immunohistochemistry of 4-HNE and 8-OHdG were performed to evaluate oxidative stress, and FSH receptor immunoreactivity was also assessed to evaluate the ovarian function. At last, we compared pregnancy numbers by mating with *C57BL/6N* male mice. As a result, in the OE group, ovarian cystic lesion was recognized as ovarian endometriosis 4 weeks after surgery. Fibrosis and iron accumulation were significantly higher in OE than other groups. Both of the oxidative stress markers were significantly elevated in the ovarian follicles of OE group. FSH receptor immunoreactivity was significantly decreased in the follicles of OE group. Finally, pregnancy number was significantly lower in the OE group.

In conclusion, we established a novel method for ovarian endometriosis mouse model. Our model would be useful for the investigation of novel drugs/procedures to prevent and cure endometriosis-associated infertility.

Research Background

Ovarian endometriosis (OE) causes not only severe menstrual pain but also infertility and an increased risk for ovarian carcinogenesis in women. Whereas peritoneal endometriosis animal models have been developed with syngeneic implantation of minced uterine tissue or genetic engineering techniques, there has been no mouse model of OE similar to human counterparts,

applicable to preclinical studies.

Research Results

Ectopic growth of endometrium was observed in association with ovary 4 weeks after implantation in 85.7 % (12/14) of the operated mice with our protocol. Mouse ovarian endometriotic lesions also involved intestine, pancreas and peritoneal wall with surrounding fibrosis and iron accumulation in its stromal layer, which is similar to human ovarian endometriosis. Iron accumulation was significantly increased in the OE group, leading to oxidative stress in each stage of the follicles as evaluated by 4-hydroxy-2-nonenal-modified proteins and 8-hydroxy-2'-deoxyguanosine. Expression of follicle stimulating hormone receptor in the follicles revealed a significant decrease during pre-antral, antral and pre-ovulatory phases in the OE group. Finally, the number of pups was significantly reduced in the OE group in comparison to the controls.

Research Summary and Future Perspective

This model affords an opportunity to evaluate agents or procedures to counteract ovarian endometriosis in the preclinical settings.

Our new mouse model with ovarian endometriosis would provide more opportunities for the basic researches on endometriosis-related infertility and ovarian cancer development.

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