News Release

Title

Phenotypic transition of endometrial fibroblasts caused by Fusobacterium infection facilitates the development of endometriosis

Key Points

- Endometriosis affects 10% of women and causes a variety of lifelong problems including pelvic pain, infertility, and cancer. Several hypotheses have been proposed to explain the cause of endometriosis.
- The treatment option of endometriosis is either hormone treatment or surgical resection, but many of the patients suffer from side effects of medicine and recurrence after surgery.
- We demonstrated transgelin (TAGLN) to be frequently upregulated in endometriosis, enhances proliferation, migration, and adhesion to peritoneal mesothelial cells, which are important in the pathogenesis of endometriosis.
- Focusing on TGF-β as an inducer of TAGLN expression, we discovered *Fusobacterium* is highly expressed in the uterus of endometriosis patients. This bacterium is also present in the oral cavity and intestinal tract, and is known to be involved in the development of colorectal cancer.
- Transvaginal infection with *Fusobacterium* was found to exacerbate endometriosis lesion formation in endometriosis mice models. Antibiotic treatment could be effective in reducing endometriotic lesions.
- Our data provided a strong and novel rationale for targeting *Fusobacterium* as a non-hormonal antibiotic treatment to treat endometriosis.

Summary

Endometriosis affects 10% of women and causes a variety of lifelong problems including pelvic pain, infertility, and cancer. Overcoming endometriosis is one of the critical issues in today's world, where the birthrate is declining. The treatment option of endometriosis is either hormone treatment or surgical resection, but many of the patients suffer from side effects of medicine and recurrence after surgery. In this study, we attempted to elucidate the pathogenic mechanism of endometriosis and to develop new therapeutic targets. First, we demonstrated transgelin (TAGLN) to be frequently upregulated in endometriosis, enhances proliferation, migration, and adhesion to peritoneal mesothelial cells, which are important in the pathogenesis of endometriosis. Focusing on TGF-β as an inducer of TAGLN expression, we

discovered *Fusobacterium* is highly expressed in the uterus of endometriosis patients. This bacterium is also present in the oral cavity and intestinal tract, and is known to be involved in the development of colorectal cancer. Transvaginal infection with *Fusobacterium* was found to exacerbate endometriosis lesion formation in endometriosis mice models. Antibiotic treatment could be effective in reducing endometriotic lesions. Our data provided a strong and novel rationale for targeting *Fusobacterium* as a non-hormonal antibiotic treatment to treat endometriosis. Currently, a specific clinical trial undergone at the Department of Obstetrics and Gynecology, Nagoya University Hospital to investigate the efficacy of antibiotic treatment for patients with endometriosis.

Research Background

Endometriosis affects 10% of women of reproductive age and causes various problems such as pelvic pain, infertility, and cancer throughout life. The treatment for endometriosis is either hormonal medication or surgical resection of the lesion, but both treatments have problems with medical side effects and a high recurrence rate after surgery. In addition, both treatments have a significant impact on pregnancy. In this study, we aim to elucidate the pathogenesis of endometriosis and to identify a novel non-hormonal therapeutic treatment for patients with endometriosis who wish to become pregnant.

Research Results

TAGLN was expressed at significantly higher levels across endometriosis fibroblasts compared to normal endometrial fibroblasts. *TAGLN* is one of the myofibroblast marker genes and enhances the proliferation, migration, and adhesion to peritoneal mesothelial cells, which are critical for the development of endometriosis. Therefore, we focused on TGF-β as an inducer of TAGLN expression and found that there is significant M2 macrophage infiltration in the uterus of endometriosis patients as TGF-β-producing cells. Furthermore, to explain the difference in macrophage infiltration, we found *Fusobacterium*, which is significantly more expressed in the uterus of endometriosis patients (Figure 1).

Infection of the mouse uterus with *Fusobacterium* exacerbated the number and weight of lesions (Figure 2), and eradication of *Fusobacterium* with a sensitive antibiotic improved lesion formation (Figure 3,4).

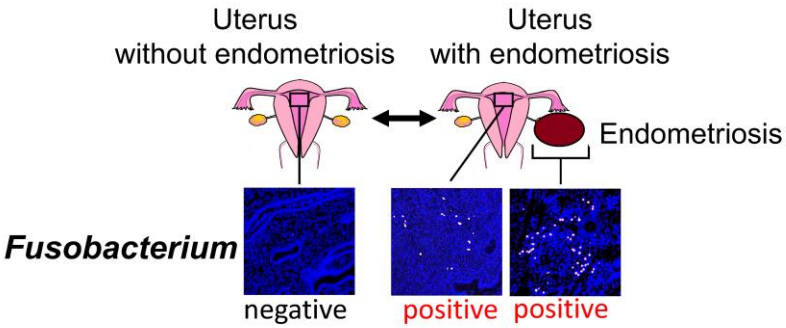

Figure 1. Discovery of the causative agent of endometriosis

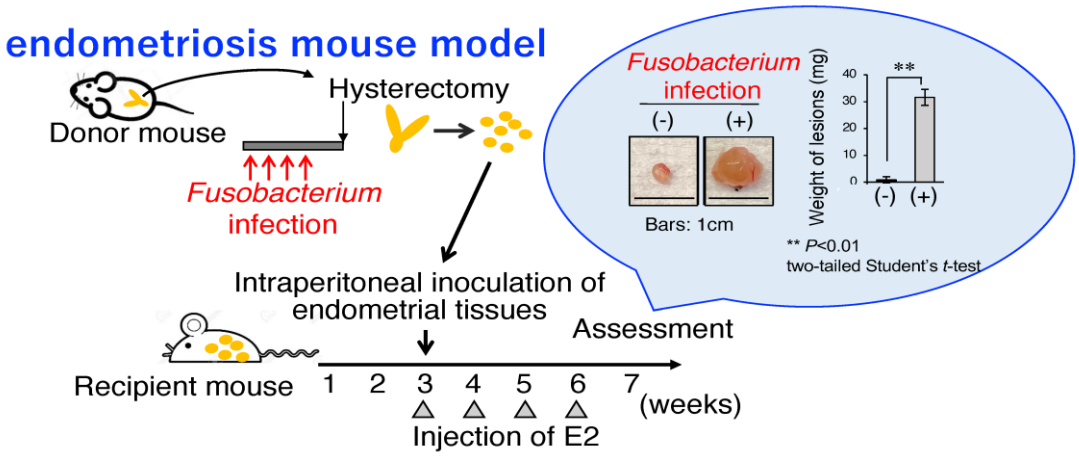

Figure 2. *Fusobacterium* enhance the endometriosis lesion formation

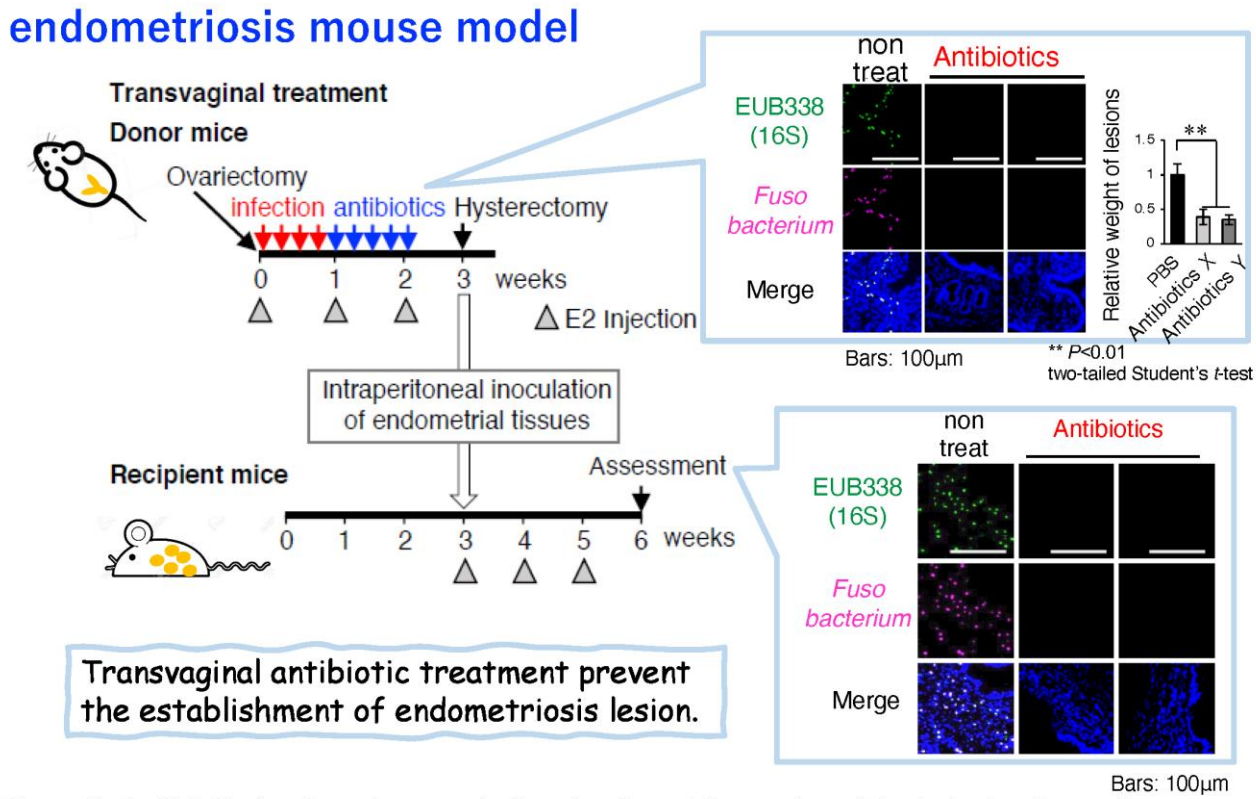

Figure 3. Antibiotic treatment prevented and reduced the endometriosis lesion formation

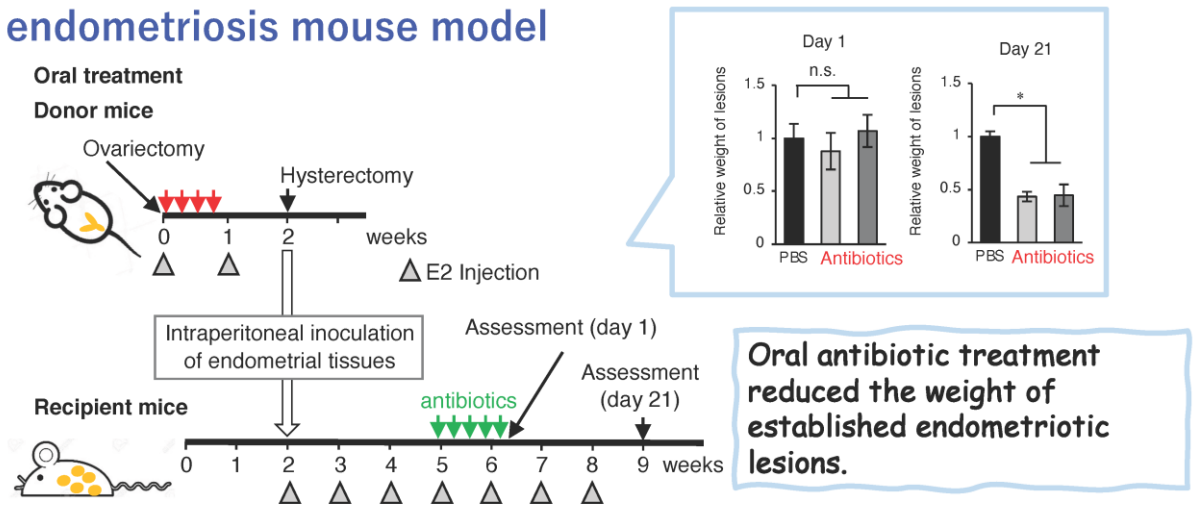

Figure 4. Antibiotic treatment prevented and reduced the endometriosis lesion formation

Research Summary and Future Perspective

In the current study, we demonstrated *Fusobacterium*-TAGLN-endometriosis axis to be frequently dysregulated in endometriosis fibroblasts. Antibiotic therapy may be a novel non-hormonal treatment strategy for patients with endometriosis in accordance with the pathogenesis of the disease (Figure 4). Currently, a specific clinical trial undergone at the Department of Obstetrics and Gynecology, Nagoya University Hospital to investigate the efficacy of antibiotic treatment for patients with endometriosis.

Publication

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Author: Ayako Muraoka[1,2], Miho Suzuki[1], Tomonari Hamaguchi[3], Shinya Watanabe[1], Kenta Iijima[1], Yoshiteru Murofushi[1], Keiko Shinjo[1], Satoko Osuka[2], Yumi Hariyama[4], Mikako Ito[3], Kinji Ohno[3], Tohru Kiyono[5], Satoru Kyo[6], Akira Iwase[7], Fumitaka Kikkawa[2], Hiroaki Kajiyama[2], and Yutaka Kondo[1,8]
Affiliation:
[1]Division of Cancer Biology, Nagoya University Graduate School of Medicine; 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
[2]Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine; 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
[3]Division of Neurogenetics, Nagoya University Graduate School of Medicine; 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
[4]Department of Obstetrics and Gynecology, Toyota Kosei Hospital; 500-1, Ihohara, Zyosui-cho, Toyota 470-0396, Japan.
[5]Project for Prevention of HPV-related Cancer, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center; Kashiwanoha 6-5-1, Kashiwa,

277-8577, Japan.
[6]Department of Obstetrics and Gynecology, Shimane University Faculty of Medicine; 89-1, Enya-Cho, Izumo 693-8501, Japan.
[7]Department of Obstetrics and Gynecology, Gunma University Graduate School of Medicine; 3-39-22 Showa-machi, Maebashi 371-8511, Japan.
[8]Institute for Glyco-core Research (iGCORE), Nagoya University; Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan.

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Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Sci_230615.pdf

This study was featured in the following publications (external links).

・Washington Post
https://www.washingtonpost.com/health/2023/06/14/endometriosis-fusobacterium-possible-links/

・Nature
https://www.nature.com/articles/d41586-023-01956-4

・New Scientist
https://www.newscientist.com/article/2378242-endometriosis-may-be-caused-by-bacterial

・Stat
https://www.statnews.com/2023/06/14/endometriosis-cause-bacteria-uterus/