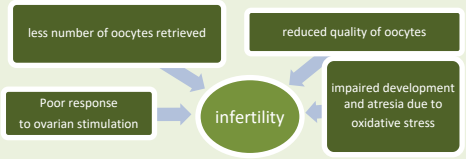
Effects of endometriotic cysts on granulosa cells

Hideaki Tanaka,Tomoko Nakamura, Tomomi Seki, Atsushi Yabuki, Reina Sonehara, Mayuko Murakami,
Sayako Yoshida, Natsuki Miyake, Ayako Muraoka, Natuki Nakanishi, Satoko Oosuka, Maki Goto, Hiroaki Kajiyama
Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine

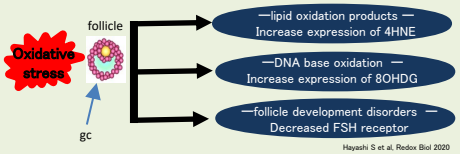
Introduction

◆ Endometriosis causes infertility



✓Infertility is associated with about 50% of ovarian endometriosis (OE) patients.
✓OE patients have less number of oocytes retrived and reduced quality of oocytes.

◆ Oxidative stress & granulosa cells (gc)



Hayashi S et al, Redox Biol 2020

✓Gc of OE model mouse expressed increased lipid oxidation products, DNA base oxidation and follicle development disorders.

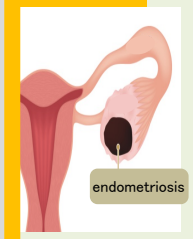
◆ Autophagy

✓Oxidative stress induces autophagy
✓Possesses cytoprotective and cytotoxic aspects
✓Excessive autophagy causes gc damage

Zhou J Int J Biol Sci 2019 · Escobar ML Apoptosis 2008; Zhou, Choi JY FS 2011 · Ming Shen AUTOPHAGY 2017

Purpose

hypothesis



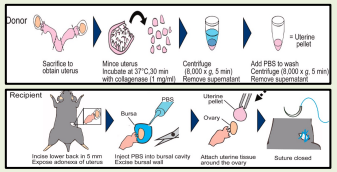
Oxidative stress → Autophagy in gc → gc damage → infertility？

We investigated the effects of OE on gc, such as autophagy with OE model mouse.

Method

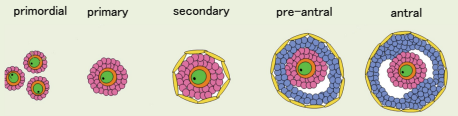
C group no treatment : **control group**
S group only injection in Bursa with PBS : **sham group**
OE group minced 9-week-old mouse uterus was treated with collagenase, pelletized and transplanted to the surface of the recipient's ovary after removing its ovarian bursa : **ovarian endometriosis group**

After 4 weeks, ovaries were collected.

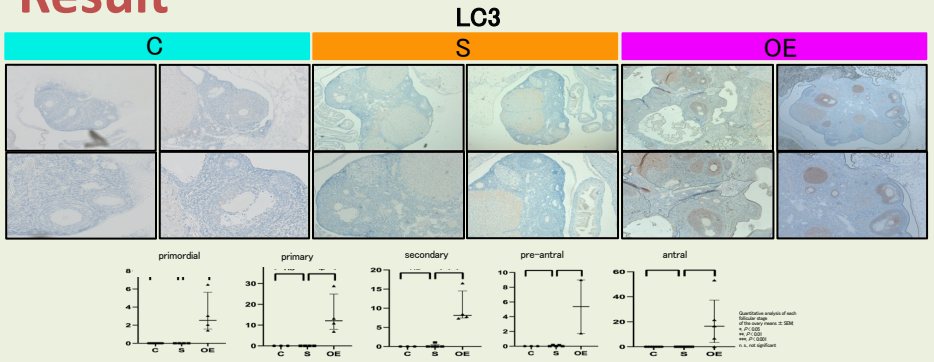


Hayashi S et al, Redox Biol 2020

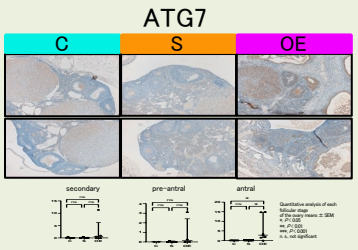
✓A total of 198 follicles of C, S, and OE were evaluated.
✓Ovarian follicles were classified into primordial, primary, secondary, preantral, and antral follicles.
✓The expressions of autophagy-related proteins (LC3, Beclin-1, and Atg7) in granulosa cells of follicles from each developmental stage were evaluated by immunostaining.



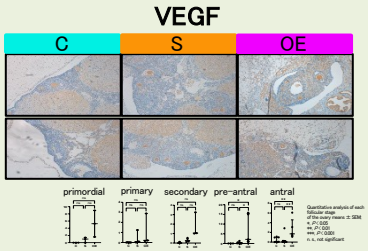
Result



・In the OE group, LC3 expression was significantly enhanced in follicular gc of all developmental stages (primordial : p=0.0001, primary : p=0.0126, secondary : p=0.0332, preantral : p=0.0098, antral : p=0.0009).



・In the OE group, ATG7 expression was significantly enhanced in antral follicles groups



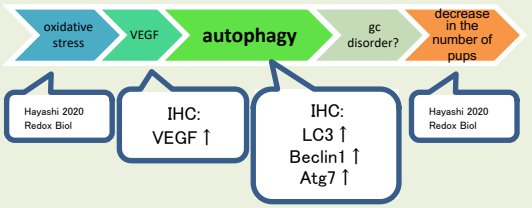
・In the OE group, VEGF expression was significantly enhanced in pre- and antral follicles groups

Conclusion

✓ In OE model mice, autophagy was suggested to be enhanced in gcs of all follicular stages.
✓ Enhanced autophagy by OE may lead to follicular damage, resulting in reduced ovarian function.

Discussion

✓ Enhanced autophagy and VEGF expression was observed in gc of OE group.
✓ VEGF / PI3K / AKT signaling is reported to regulate autophagy in bovine gc. Lizhu Ma et al, Reproduction 2019
✓ Enhanced autophagy in gc of OE may exert cytotoxic effects and lead to infertility.
✓ Our results suggest that VEGF-regulated autophagy may be involved in OE model mice.



SEUD Congress 2021
COI Disclosure

Nothing to declare

Name of First Author : Hideaki Tanaka