Upregulation of autophagy in ovarian endometriosis

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Endometriosis: definition

Endometriosis is a common gynecologic disease affecting 8-10% of fertile women, characterized by pelvic lesions associated with pain and infertility.
Starting from retrograde menstruation, several hypotheses have been done, but nowadays a unifying theory regarding the origin of endometriosis still remains indefinite.

The most recent proposals suggest that ectopic endometrial implants are the result of lymphatic or hematogenous dissemination of endometrial cells.

In the last years some study suggest that extrauterine stem-progenitor cells originating from bone marrow may differentiate into endometriotic tissue.
Endometriosis: pathogenesis

1. Impaired apoptosis
2. Increased oxidative stress
3. Increased cell proliferation
4. Acute inflammation
5. Invasion
6. Neoangiogenesis
7. Neurogenesis

Eutopic Endometrium
Hormones
Cell proliferation
Inflammation

infertility
pain
chronic inflammation
Autophagy is a complex catabolic process through which cellular organelles, macromolecules and intracellular pathogens are sequestered in autophagosomes and degraded by lysosomes.

Survival mechanism contributing to maintain cellular homeostasis under stress-induced conditions.

decreased susceptibility to apoptosis

persistent oxidative stress
Aim of the study

To investigate the occurrence of the autophagic process in ovarian endometriotic lesions

To understand the mechanisms involved in the regulation of the autophagic process
Materials and methods

Samples were obtained from women undergoing laparoscopic treatment for pain or infertility

The cyst diameter measured by US ranged from 20 to 80 mm

All patients showed stage III or IV of endometriosis

Endometriosis group:
- ovarian endometriotic cysts tissues (OMA); n = 13
- their eutopic endometrium (EEOMA); n = 13

Non endometriosis group:
- normal endometrial tissues (NE); n = 18

Exclusion criteria: hormonal treatment in the last 3 months
Results: biochemical markers (LC3-II and p62)

LC3-II is the most widely used biomarker of autophagosome formation.

P62 is an ubiquitin-binding protein and it is itself degraded by autophagy.

LC3-II and the ratio LC3b-II/LC3-I are significantly higher in OMA.

A decline in p62 levels indicates an increase of autophagic process in OMA.

Biochemical markers of autophagy indicates that autophagy is up-regulated in OMA.

Fertil Steril, 2015
Results: autophagy-related genes

ATG14 and BECN1 code for two major components necessary for autophagic membrane nucleation and autophagosome-lysosome fusion.

ATG7 and LC3 genes are both necessary for membrane expansion and closure.

Autophagy-related genes are up-regulated in OMA.
Results: p53 and bcl-2

**p53** is a tumor suppressor protein that induces apoptotic cells death.

**bcl-2** is an oncoprotein that inhibits apoptotic cell death.

- **p53** is significantly down-regulated in OMA if compared with other groups.

- **bcl-2** is slightly but significantly down-regulated in OMA.
Results: HO-1

Endometriotic cells experienced a persistent condition of oxidative stress.

HO-1 is a limiting enzyme in heme degradation, highly inducible by oxidative stress and inflammation.

In OMA the expression of HO-1 is up-regulated and it is undetectable or very low in NE and in the eutopic endometrium.
Conclusions

In ovarian endometriomas the autophagic process is up-regulated contributing to survival of endometriotic cells in ectopic sites and to lesions maintenance.

The decreased susceptibility to apoptosis and the persistent oxidative stress experienced by endometriotic cells could favor autophagy stimulation.
Thank you