

# Accepted Manuscript

Autophagy in endometriosis: Friend or foe?

Lei Zhan, Jun Li, Bing Wei

PII: S0006-291X(17)32130-7

DOI: [10.1016/j.bbrc.2017.10.145](https://doi.org/10.1016/j.bbrc.2017.10.145)

Reference: YBBRC 38762

To appear in: *Biochemical and Biophysical Research Communications*

Received Date: 23 October 2017

Accepted Date: 27 October 2017

Please cite this article as: L. Zhan, J. Li, B. Wei, Autophagy in endometriosis: Friend or foe?, *Biochemical and Biophysical Research Communications* (2017), doi: 10.1016/j.bbrc.2017.10.145.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**Autophagy in endometriosis: friend or foe?**Lei Zhan<sup>1</sup>, Jun Li<sup>2</sup> and Bing Wei<sup>1\*</sup>

<sup>1</sup>Department of gynecology and obstetrics, The Second Affiliated Hospital of Anhui Medical University, 678 Fu Rong Road, Hefei 230601, China

<sup>2</sup> School of Pharmacy, Anhui Key Laboratory of Bioactivity of Natural Products, Anhui Medical University, Meishan Road No. 81, 230032 Hefei, China.

\*Correspondence to: Bing Wei;

E-mail address: m1351565@163.com

**Abbreviations:** 3-MA, 3-methyladenine; ERK, extracellular signal-regulated kinase; MIS, Mullerian inhibiting substance; mTOR, Mammalian target of rapamycin; NF- $\kappa$ B, nuclear factor-k-gene binding  $\kappa$ ; OH-1, heme oxygenase-1; TRPV, transient receptor potential vanilloid type

**Abstract**

Endometriosis is a chronic, estrogen-dependent disease and characterized by the implantation of endometrial glands and stroma deep and haphazardly into the outside the uterine cavity. It affects an estimated 10% of the female population of reproductive age and results in obvious reduction in health-related quality of life. Unfortunately, there is no a consistent theory for the etiology of endometriosis. Furthermore, the endometriosis is hard to diagnose in early stage and the treatment methods are limited. Importantly, emerging evidence has investigated that there is a close relationship between endometriosis and autophagy. However, autophagy is a friend or foe in endometriosis is puzzling, the precise mechanism underlying autophagy in endometriosis has not been fully elucidated yet. Here, we provide an integrated view on the acquired findings of the connections between endometriosis and autophagy. We also discuss which may contribute to the abnormal level of autophagy in endometriosis.

**KEYWORDS:** Autophagy; endometriosis; friend; foe; mechanism

## **Introduction**

Endometriosis is defined as the presence of functional uterine glands and stroma outside the uterine cavity including ovaries and pelvic peritoneum, rectovaginal septum. Endometriosis is an estrogen-dependent disorder of the women reproductive tract and the third leading cause of gynecologic hospitalization in the USA [1,2]. It is indicated that endometriosis is one of the most common causes of chronic pelvic pain, infertility, dysmenorrhea, dyspareunia, dysuria and dyschezia, and affects an estimated 10% of the female population of reproductive age and 20-50% of infertile women [3,4,5]. There are several theories have been proposed underlying the pathogenesis of endometriosis. Among the various views, Sampson's theory of retrograde menstruation is the most widely accepted because it was observed that retrograde menstruation occurs in up to 90% of all women [6,7]. Sampson's theory described that the menstrual debris travels not only anterogradely to the vagina, but also through the fallopian tube into the peritoneal cavity in a retrograde manner and implants in the dependent areas of peritoneum during menstruation [6,7]. Actually, as studies continued, it was acceptable that the pathogenesis of endometriosis is polyfactorial which involved in reflux menstruation, hormonally mediated proliferation and apoptosis [8,9,10], hematologic spread, inflammation, immune response and genetic factors [2].

Autophagy is a pathway by which cytoplasmic components, including intracellular soluble macromolecules, organelles and microorganisms, is delivered to lysosomes for degradation [11]. Studies supported that autophagy exists at basal level in all cell types. However, defects in autophagy underlie the pathogenesis of many diseases. It is worth mentioning in advance that autophagy is proved to act as a double-edged sword in multiple diseases which depend on different context [12]. In these years, accumulating researches present potential evidence that the progression of

endometriosis was crucially implicated in autophagy, and seemingly opposing concepts concerning the role of autophagy in endometriosis have been proposed, with evidence that autophagy was up or down-regulated in endometriosis [5,13]. So autophagy in endometriosis: friend or foe? In this mini review, we aim to explore and summarize the latent mechanism of autophagy in endometriosis from the recent studies and discuss which may contribute to the abnormal level of autophagy in endometriosis.

### **Autophagy as friend in endometriosis**

The relevance of autophagy to endometriosis was observed as early as 1986 by Cornillie et al. [14], they found the lysosomal autophagy was accelerated in 11 patients after treatment with antiprogestosterone in 20 infertile patients who with endometriotic implants [14]. Several years before, researches revealed an apparent connection of endometriosis with Beclin-1 [15,16]. It was indicated that the level of Beclin-1 mRNA and protein were prominently lower in cultured stromal cells of eutopic endometrial and endometrial tissues of endometriosis compared to endometriosis-free patients. Beclin-1 protein expression was negatively correlated with serum CA-125 level and pelvic pain, suggesting low level of Beclin-1 might contribute to the development of endometriosis [15,16]. But there are no distinct statistical differences of Beclin-1 expression between eutopic and ectopic endometriotic in endometriosis [16]. Choi et al. suggested that the attenuation of autophagy in the secretory phase of endometriotic tissues was caused by the increased mTOR activity. Treatment with the mTOR inhibitor rapamycin induced LC3-II expression, while the effect of rapamycin was reversed by the addition of autophagy inhibitor 3-methyladenine (3-MA) [17]. They also defined that dienogest could enhance autophagy induction and inhibit AKT, extracellular signal-regulated kinase (ERK), mammalian target of rapamycin (mTOR) signaling in estrogen-treated endometriotic stromal cells. Incubation of estrogen-treated endometriotic stromal cells with AKT and ERK1/2 inhibitors increased LC3-II and cleaved caspase-3 expression.

In addition, endometriotic stromal cells treated with dienogest and estrogen shown significantly increased expression of LC3-II and cleaved caspase-3 compared with endometriotic stromal cells cultured in estrogen alone, and this dienogest-mediated increase in LC3-II and cleaved caspase-3 expression was statistically decreased by the addition of the autophagy inhibitor 3-MA. These findings indicated that dienogest treatment in estrogen-treated endometriotic cells could induce autophagy by suppressing AKT/mTOR and ERK/mTOR activity, further promote apoptosis in endometriosis [17]. Notably, both of the two studies recognized that treatment with estrogen and progesterone failed to change LC3-II expression in endometriotic cell [5,17]. Another possible mechanism of autophagy down-regulated in the pathogenesis of endometriosis was delineated by Mei et al. [18] Firstly, they validated the ER $\alpha$  and p62 were significantly up-regulated, and LC3-II, Beclin-1 and PR were down-regulated in eutopic and ectopic secretory phase endometrial stromal cells compared with normal secretory phase endometrial stromal cells. In consistent with Choi et al. results [5], Mei and colleagues found the level of autophagy was not changed during menstrual cycle in ectopic endometrium from endometriosis patients [18]. But inconsistent with Ren et al. results [16], Mei et al. investigated the level of Beclin-1 was lower in ectopic secretory phase endometrial stromal cells than in eutopic secretory phase endometrial stromal cells [18]. They also implied that the suppression of autophagy caused by estrogen is dependent on CXCL12-CXCR4 interaction, and CXCL12 inhibited the autophagy of secretory phase endometrial stromal cells was *via* activating the nuclear factor-k-gene binding (NF- $\kappa$ B) signaling pathway [18]. Later on, these authors further suggested that down-regulation of autophagy in endometriosis may promote the reactivity of endometrial stromal cells to the IL-15, which could promote growth and invasion of endometrial stromal cells [19]. In an experiment *in vitro* by Borahay et al. suggested that Mullerian inhibiting substance (MIS) promoting autophagy as well as apoptosis in ectopic endometrial cell lines [20].

### **Autophagy as foe in endometriosis**

Paradoxically, in another study lately, Giulia and co-workers defined autophagy was up-regulated (increase of lipidated LC3-II protein levels and LC3-II/LC3-I ratio, decrease of p62 expression, induction of LC3B, ATG14, beclin-1, ATG7 genes) in ovarian endometriosis compared with eutopic endometria of affected or healthy women [13]. They delineated two mechanisms which can be responsible for autophagy stimulation in ovarian endometriosis, one is the decreased susceptibility to p53 protein, which in turn is controlled by autophagy, the other one is the increased expression of oxygenase-1 (OH-1) protein, which exhibited persistent oxidative stress and could favor autophagy stimulation in endometriotic cells [13]. It has been clearly identified that hypoxia acted as a promoter in the development in endometriosis [21,22]. A *in vitro* study showed a novel mechanism underlying up-regulation of autophagy in endometriosis, they suggested that hypoxia responsive miR-210 over-expression contributed to high level of autophagy in ovarian endometriotic cell line CRL-7566 by inhibiting Bcl-2 expression [23]. In line therewith, a recent study by Liu et al. suggested that HIF-1 $\alpha$  promoted human endometrial stromal cells (HESCs) invasion and metastasis by upregulating autophagy, inhibiting autophagy with specific inhibitors with 3-MA and CQ and Beclin1 siRNA attenuated hypoxia triggered migration and invasion of HESCs [24]. Most important, Nanjundan et al. noted that the autophagic flux inhibitor hydroxychloroquine (HCQ) could reduce the *in vitro* survival capacity of human endometriotic, decrease lesion numbers, and disrupt lesion histopathology in a mouse model of endometriosis, indicating that inhibition of autophagy could be potential therapeutic strategy approach for endometriosis [25].

### **Which contributes to the abnormal level of autophagy in endometriosis?**

Now we know that the abnormal level of autophagy in endometriosis is controversial, the down-regulation of autophagy in endometriosis is estrogen-dependent [26]. Inflammation also causes autophagy down-regulated in endometriosis [18],[19]. Persistent oxidative stress experienced, decreased susceptibility to p53 and hypoxia

contribute to autophagy increasing in endometriosis [13]. Even though, there are a multitude of potential factors which may lead to abnormal regulation of autophagy in endometriosis. For example, angiogenesis were inevitable course in the development of endometriosis [27,28]. Angiogenesis is known as important regulator to autophagy in a plethora of diseases [29,30]. But whether and how angiogenesis cause the changes of autophagy in endometriosis remain unclear. In addition, ions channel is recognized to exert crucial roles in endometriosis. For example, transient receptor potential vanilloid type 1 (TRPV1)-mediated  $\text{Ca}^{2+}$  influx is investigated to be association with chronic pelvic pain in the peritoneal endometriosis foci of women [31,32]. Interestingly, it is clearly that  $\text{Ca}^{2+}$  signals play a major role in regulating autophagy [33,34,35]. Also, our study indicates that TRPV4, which is well known as a highly  $\text{Ca}^{2+}$ -permeable non-selective cation channel, is essential for autophagy induction [36]. It was well accepted that iron overload was found in endometriosis and played a key function in endometriosis pathogenesis [37,38]. A recent study prompts that iron was rich expressed in the cyst fluid of endometriosis-associated ovarian cancers, and iron modulate cell death in a Ras- and MAPK-dependent mitochondrial damage in ovarian cancer cells with increases in LC3-II levels [39,40]. But whether iron plays a function in autophagy in endometriosis need further determined.

### **Conclusion and perspectives**

From all these studies, it is clear that there is an intimate relationship between autophagy and endometriosis (Figure 1). But autophagy in endometriosis: friend or foe? One the one hand, researches observe a down-regulation of autophagy in endometriosis. The related mechanism is implicated in the inhibition of mTOR by PI3K/AKT signaling pathway. Furthermore, the suppression of autophagy by CXCL12-dependent NF- $\kappa$ B pathway also contributes to endometriosis. In addition, the drugs use for endometriosis treatment is involved in the enhancing of autophagy. One the other hand, up-regulation of autophagy in endometriosis also is observed by

studies. Hypoxia, decreased susceptibility to p53 and high expression of OH-1 contribute to the autophagy up-regulation. Besides, angiogenesis, ions channel, and iron may exert functions in autophagy in endometriosis. It is worthy mentioned that autophagy seems unchanged during menstrual cycle in endometriosis. Nevertheless, autophagy is a friend or foe in endometriosis is puzzling. In view of the results of these studies included only a handful of samples, further studies are required to investigate the exact role of autophagy in endometriosis, especially the *in vivo* studies and more autophagy-related protein should be detected. Moreover, using autophagy inhibitor will be contributed to confirm the exact role of autophagy in endometriosis.

### Acknowledgements

The work was supported by the National Science Foundation of China (Nos. 81273526, 81473268) and Natural Science Foundation of Colleges and Universities (Nos. KJ2017A197)

### Disclosure statement

The authors report no conflicts of interests

### References

- [1] M.T. McLennan, A. Steele, F.C. Leong, Obstetrics and Gynecology Clinics of North America. Pelvic pain in women. Preface, Obstet Gynecol Clin North Am 41 (2014) xiii-xiv.
- [2] A. Laux-Biehlmann, T. d'Hooghe, T.M. Zollner, Menstruation pulls the trigger for inflammation and pain in endometriosis, Trends Pharmacol Sci 36 (2015) 270-276.
- [3] K.E. Nnoaham, L. Hummelshoj, P. Webster, T. d'Hooghe, F. de Cicco Nardone, C. de Cicco Nardone, C. Jenkinson, S.H. Kennedy, K.T. Zondervan, c. World Endometriosis Research Foundation Global Study of Women's Health, Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries, Fertil Steril 96 (2011) 366-373 e368.
- [4] D. LeRoith, Endocrinology and Metabolism Clinics of North America. HIV and endocrine disorders. Foreword, Endocrinol Metab Clin North Am 43 (2014) xiii-xv.
- [5] J. Choi, M. Jo, E. Lee, H.J. Kim, D. Choi, Differential induction of autophagy by mTOR is associated with abnormal apoptosis in ovarian endometriotic cysts, Mol Hum Reprod 20 (2014) 309-317.
- [6] J.A. Sampson, Metastatic or Embolic Endometriosis, due to the Menstrual Dissemination of



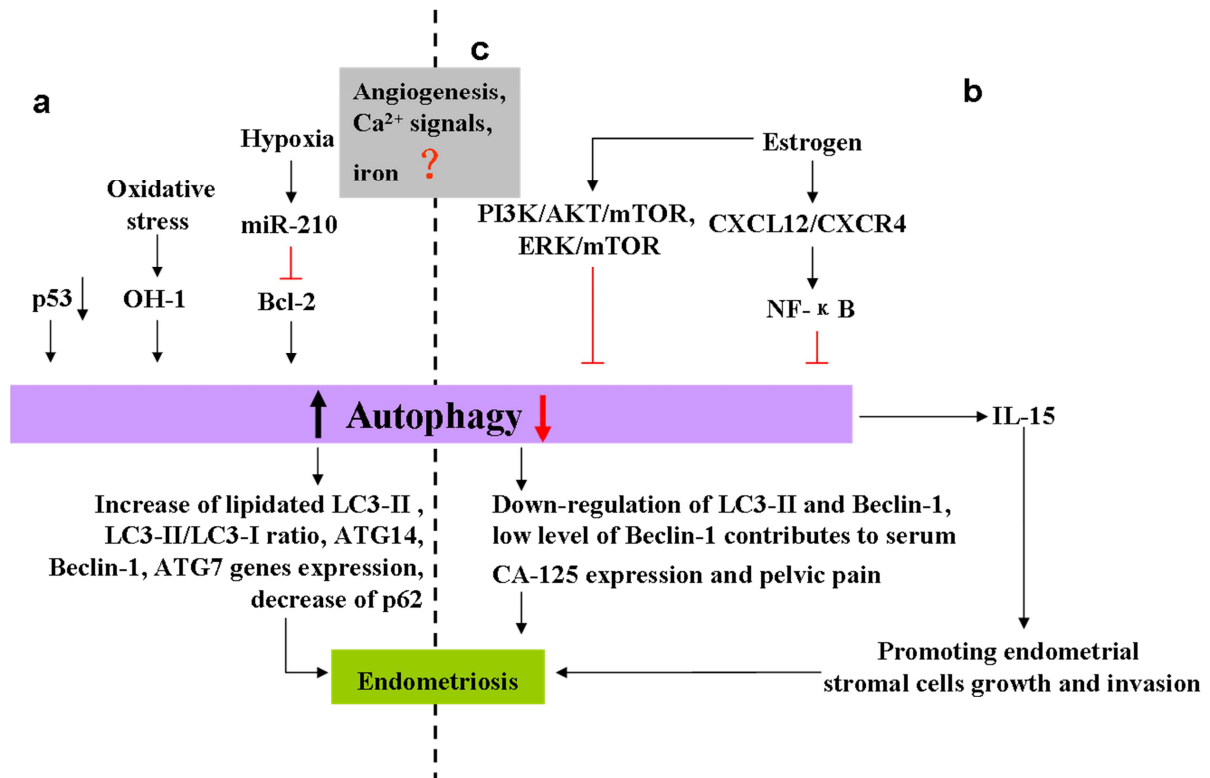
- Endometrial Tissue into the Venous Circulation, *Am J Pathol* 3 (1927) 93-110 143.
- [7] S.F. Lindsay, D.E. Luciano, A.A. Luciano, Emerging therapy for endometriosis, *Expert Opin Emerg Drugs* 20 (2015) 449-461.
- [8] L. Carvalho, S. Podgaec, M. Bellodi-Privato, T. Falcone, M.S. Abrao, Role of eutopic endometrium in pelvic endometriosis, *J Minim Invasive Gynecol* 18 (2011) 419-427.
- [9] K. Chwalisz, M.C. Perez, D. Demanno, C. Winkel, G. Schubert, W. Elger, Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis, *Endocr Rev* 26 (2005) 423-438.
- [10] R. Shao, S. Cao, X. Wang, Y. Feng, H. Billig, The elusive and controversial roles of estrogen and progesterone receptors in human endometriosis, *Am J Transl Res* 6 (2014) 104-113.
- [11] L. Zhan, Y. Zhang, W. Wang, E. Song, Y. Fan, J. Li, B. Wei, Autophagy as an emerging therapy target for ovarian carcinoma, *Oncotarget* 7 (2016) 83476-83487.
- [12] N. Mizushima, M. Komatsu, Autophagy: renovation of cells and tissues, *Cell* 147 (2011) 728-741.
- [13] G. Allavena, P. Carrarelli, B. Del Bello, S. Luisi, F. Petraglia, E. Maellaro, Autophagy is upregulated in ovarian endometriosis: a possible interplay with p53 and heme oxygenase-1, *Fertil Steril* 103 (2015) 1244-1251 e1241.
- [14] F.J. Cornillie, I.A. Brosens, G. Vasquez, I. Riphagen, Histologic and ultrastructural changes in human endometriotic implants treated with the antiprogestosterone steroid ethynorgestrienone (gestrinone) during 2 months, *Int J Gynecol Pathol* 5 (1986) 95-109.
- [15] L. Zhang, Y. Liu, Y. Xu, H. Wu, Z. Wei, Y. Cao, The expression of the autophagy gene beclin-1 mRNA and protein in ectopic and eutopic endometrium of patients with endometriosis, *Int J Fertil Steril* 8 (2015) 429-436.
- [16] Y. Ren, L. Mu, X. Ding, W. Zheng, Decreased expression of Beclin 1 in eutopic endometrium of women with adenomyosis, *Arch Gynecol Obstet* 282 (2010) 401-406.
- [17] J. Choi, M. Jo, E. Lee, D.Y. Lee, D. Choi, Dienogest enhances autophagy induction in endometriotic cells by impairing activation of AKT, ERK1/2, and mTOR, *Fertil Steril* 104 (2015) 655-664 e651.
- [18] J. Mei, X.Y. Zhu, L.P. Jin, Z.L. Duan, D.J. Li, M.Q. Li, Estrogen promotes the survival of human secretory phase endometrial stromal cells via CXCL12/CXCR4 up-regulation-mediated autophagy inhibition, *Hum Reprod* 30 (2015) 1677-1689.
- [19] J.J. Yu, H.T. Sun, Z.F. Zhang, R.X. Shi, L.B. Liu, W.Q. Shang, C.Y. Wei, K.K. Chang, J. Shao, M.Y. Wang, M.Q. Li, IL-15 promotes growth and invasion of ESC and inhibits killing activity of NK cell in endometriosis, *Reproduction* (2016).
- [20] M.A. Borahay, F. Lu, B. Ozpolat, I. Tekedereli, B. Gurates, S. Karipcin, G.S. Kilic, Mullerian inhibiting substance suppresses proliferation and induces apoptosis and autophagy in endometriosis cells in vitro, *ISRN Obstet Gynecol* 2013 (2013) 361489.
- [21] L. Zhan, W. Wang, Y. Zhang, E. Song, Y. Fan, B. Wei, Hypoxia-inducible factor-1alpha: A promising therapeutic target in endometriosis, *Biochimie* 123 (2016) 130-137.
- [22] Y. Xiong, Y. Liu, W. Xiong, L. Zhang, H. Liu, Y. Du, N. Li, Hypoxia-inducible factor 1alpha-induced epithelial-mesenchymal transition of endometrial epithelial cells may contribute to the development of endometriosis, *Hum Reprod* 31 (2016) 1327-1338.
- [23] T.X. Xu, S.Z. Zhao, M. Dong, X.R. Yu, Hypoxia responsive miR-210 promotes cell survival and autophagy of endometriotic cells in hypoxia, *Eur Rev Med Pharmacol Sci* 20 (2016) 399-406.
- [24] H. Liu, Z. Zhang, W. Xiong, L. Zhang, Y. Xiong, N. Li, H. He, Y. Du, Y. Liu, Hypoxia-inducible

- factor-1alpha promotes endometrial stromal cells migration and invasion by upregulating autophagy in endometriosis, *Reproduction* 153 (2017) 809-820.
- [25] A. Ruiz, S. Rockfield, N. Taran, E. Haller, R.W. Engelman, I. Flores, P. Panina-Bordignon, M. Nanjundan, Effect of hydroxychloroquine and characterization of autophagy in a mouse model of endometriosis, *Cell Death Dis* 7 (2016) e2059.
- [26] J. Choi, M. Jo, E. Lee, D.Y. Lee, D. Choi, Dienogest enhances autophagy induction in endometriotic cells by impairing activation of AKT, ERK1/2, and mTOR, *Fertil Steril* (2015).
- [27] G. Goteri, G. Lucarini, N. Montik, A. Zizzi, D. Stramazotti, G. Fabris, A.L. Tranquilli, A. Ciavattini, Expression of vascular endothelial growth factor (VEGF), hypoxia inducible factor-1alpha (HIF-1alpha), and microvessel density in endometrial tissue in women with adenomyosis, *Int J Gynecol Pathol* 28 (2009) 157-163.
- [28] M. Lamp, M. Saare, T. Laisk, H. Karro, U. Kadastik, A. Metspalu, M. Peters, A. Salumets, Genetic variations in vascular endothelial growth factor but not in angiotensin I-converting enzyme genes are associated with endometriosis in Estonian women, *Eur J Obstet Gynecol Reprod Biol* 153 (2010) 85-89.
- [29] C.K. Domigan, C.M. Warren, V. Antanesian, K. Happel, S. Ziyad, S. Lee, A. Krall, L. Duan, A.X. Torres-Collado, L.W. Castellani, D. Elashoff, H.R. Christofk, A.M. van der Blik, M. Potente, M.L. Iruela-Arispe, Autocrine VEGF maintains endothelial survival through regulation of metabolism and autophagy, *J Cell Sci* 128 (2015) 2236-2248.
- [30] H. Wang, Y. Wang, D. Li, Z. Liu, Z. Zhao, D. Han, Y. Yuan, J. Bi, X. Mei, VEGF inhibits the inflammation in spinal cord injury through activation of autophagy, *Biochem Biophys Res Commun* 464 (2015) 453-458.
- [31] M.G. Rocha, J.C. e Silva, A. Ribeiro da Silva, F.J. Candido Dos Reis, A.A. Nogueira, O.B. Poli-Neto, TRPV1 expression on peritoneal endometriosis foci is associated with chronic pelvic pain, *Reprod Sci* 18 (2011) 511-515.
- [32] O.B. Poli-Neto, A.A. Filho, J.C. Rosa e Silva, F. Barbosa Hde, F.J. Candido Dos Reis, A.A. Nogueira, Increased capsaicin receptor TRPV1 in the peritoneum of women with chronic pelvic pain, *Clin J Pain* 25 (2009) 218-222.
- [33] A.J. Liu, S.H. Wang, S.Y. Hou, C.J. Lin, W.T. Chiu, S.H. Hsiao, T.H. Chen, C.M. Shih, Evodiamine Induces Transient Receptor Potential Vanilloid-1-Mediated Protective Autophagy in U87-MG Astrocytes, *Evid Based Complement Alternat Med* 2013 (2013) 354840.
- [34] I.X. McLeod, Y.W. He, Editorial: TRPV1: how thymocytes sense stress and respond with autophagy, *J Leukoc Biol* 92 (2012) 409-411.
- [35] J.P. Decuyper, J.B. Parys, G. Bultynck, ITPRs/inositol 1,4,5-trisphosphate receptors in autophagy: From enemy to ally, *Autophagy* 11 (2015) 1944-1948.
- [36] L. Zhan, Y. Yang, T.T. Ma, C. Huang, X.M. Meng, L. Zhang, J. Li, Transient receptor potential vanilloid 4 inhibits rat HSC-T6 apoptosis through induction of autophagy, *Mol Cell Biochem* 402 (2015) 9-22.
- [37] C.P. Alvarado-Diaz, M.T. Nunez, L. Devoto, R. Gonzalez-Ramos, Iron overload-modulated nuclear factor kappa-B activation in human endometrial stromal cells as a mechanism postulated in endometriosis pathogenesis, *Fertil Steril* 103 (2015) 439-447.
- [38] A.F. Vanin, L.V. Adamian, E.N. Burgova, N.A. Tkachev, [Physico-chemistry of dinitrosyl iron complexes with thiol-containing ligands underlying their beneficial treatment of endometriosis], *Biofizika* 59 (2014) 766-775.

- [39] K.A. Bauckman, E. Haller, I. Flores, M. Nanjundan, Iron modulates cell survival in a Ras- and MAPK-dependent manner in ovarian cells, *Cell Death Dis* 4 (2013) e592.
- [40] K. Bauckman, E. Haller, N. Taran, S. Rockfield, A. Ruiz-Rivera, M. Nanjundan, Iron alters cell survival in a mitochondria-dependent pathway in ovarian cancer cells, *Biochem J* 466 (2015) 401-413.

### Figure legends

**Fig. 1** Mechanism underlying autophagy in endometriosis. **a:** Autophagy is up-regulated in endometriosis (increase of lipidated LC3-II , LC3-II/LC3-I ratio, ATG14, Beclin-1, ATG7 genes expression, decrease of p62). p53 deletion in endometriosis contributes to autophagy up-regulation. Oxidative stress-mediated OH-1 over-expression and hypoxia responsive miR-210 over-expression contribute to high level of autophagy. **b:** Down-regulation of autophagy in endometriosis is estrogen-dependent (down-regulation of LC3-II and Beclin-1). Activation of PI3K/AKT/mTOR and ERK/mTOR caused autophagy down-regulation. CXCL12/CXCR4-mediated NF- $\kappa$ B over-expression contributes to low level of autophagy in endometriosis. **c:** Whether and how angiogenesis, Ca<sup>2+</sup> signals, and iron cause the abnormal levels of autophagy in endometriosis remain unclear.



Autophagy was crucially connective with endometriosis;

The role of autophagy in endometriosis is controversial;

Autophagy is a friend in endometriosis;

Autophagy is a foe in endometriosis

ACCEPTED MANUSCRIPT