Am J Transl Res 2017;9(11):4707-4725
www.ajtr.org /ISSN:1943-8141/AJTR0055984

Review Article

Autophagy in endometriosis

Hui-Li Yang[1,2,3], Jie Mei[4], Kai-Kai Chang[1], Wen-Jie Zhou[1], Li-Qing Huang[5], Ming-Qing Li[1,2,3]

[1]Insititute of Obstetrics and Gynecology, Hospital of Obstetrics and Gynecology, Fudan University, Shanghai 200011, People's Republic of China; [2]Key Laboratory of Reproduction Regulation of NPFPC, SIPPR, IRD, Fudan University, Shanghai 200032, People's Republic of China; [3]Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Shanghai 200011, People's Republic of China; [4]Department of Obstetrics and Gynecology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, Jiangsu, People's Republic of China; [5]Department of Statistics and Psychology, College of Letters and Science, University of California Davis, Davis, CA 95618, USA

Received February 3, 2017; Accepted September 23, 2017; Epub November 15, 2017; Published November 30, 2017

Abstract: Endometriosis (EMS) is a common gynecologic disease that causes chronic pelvic pain, dysmenorrhea, and infertility in women. The doctrine of menstruation back flow planting and defects in the immune system are well known and widely accepted. In recent years, increasing studies have been focused on the role of autophagy in EMS, and have shown that autophagy plays a vital role in EMS. Autophagy, which is known as the non-apoptotic form of programmed cell death induced by a large number of intracellular/extracellular stimuli, is the major cellular pathway for the degradation of long-lived proteins and cytoplasmic organelles in eukaryotic cells. Autophagy commonly refers to macroautophagy, which is characterized by autophagosomes (double-membrane vesicles). In normal endometrial tissues, autophagy is induced in glandular epithelial and stromal cells throughout the menstrual cycle. However, aberrant autophagy occurs in the eutopic endometrium and ectopic endometriotic foci, which contributes to the pathogenesis of EMS by promoting the hyperplasia of endometriotic tissues and stromal cells, restricting apoptosis, and inducing abnormal immune responses. Consistent with changes in autophagy levels between normal endometria, eutopic and ectopic endometria from patients with EMS, the altered expression of autophagy-related genes (ATGs) is also observed. Currently, many factors are involved in the aberrant autophagy of endometriotic tissues, including female hormones, certain drugs, hypoxia, and oxidative stress. Therefore, studies focusing on autophagy may uncover a new potential treatment for EMS. The aim of this review is to discuss the role of aberrant autophagy in EMS and to explore the potential value of autophagy as a target for EMS therapy.

Keywords: Autophagy, endometriosis, autophagy-related genes, endometrial stromal cells

Introduction

Endometriosis (EMS) is a common gynecologic disease affecting approximately 5-15% of all women of reproductive age and 20-50% of all infertile women [1, 2], and it is one of the most common causes of chronic pelvic pain, dysmenorrhea and infertility [3, 4]. EMS is characterized by the presence, transfer, invasion, and cultivation of growing endometrial tissue outside of the uterine cavity [5]. Some hypotheses have been proposed to explain the migration, implantation and survival of the ectopic endometrial tissue and stroma, such as retrograde menstrual reflux [6], ectopic presence of endometrial stem cells [7] and defects in the immune system [8].

As shown in the recent study by Choi *et al.* [9], the induction of autophagy exerts a pro-apoptotic effect on normal human endometrial cells. EMS-derived endometrial tissues are characterized by reduced autophagy compared with the normal endometrium [10]. Autophagy is dysregulated in the uterine horns and eutopic endometria of mice with induced EMS and autophagic markers are differentially expressed compared with control mice [11]. Based on accumulating evidences, the level of autophagy is most likely associated with the pathogenesis of EMS.

Therefore, this paper is the first to systematically review the accumulating evidence and mechanisms reported in human and experi-

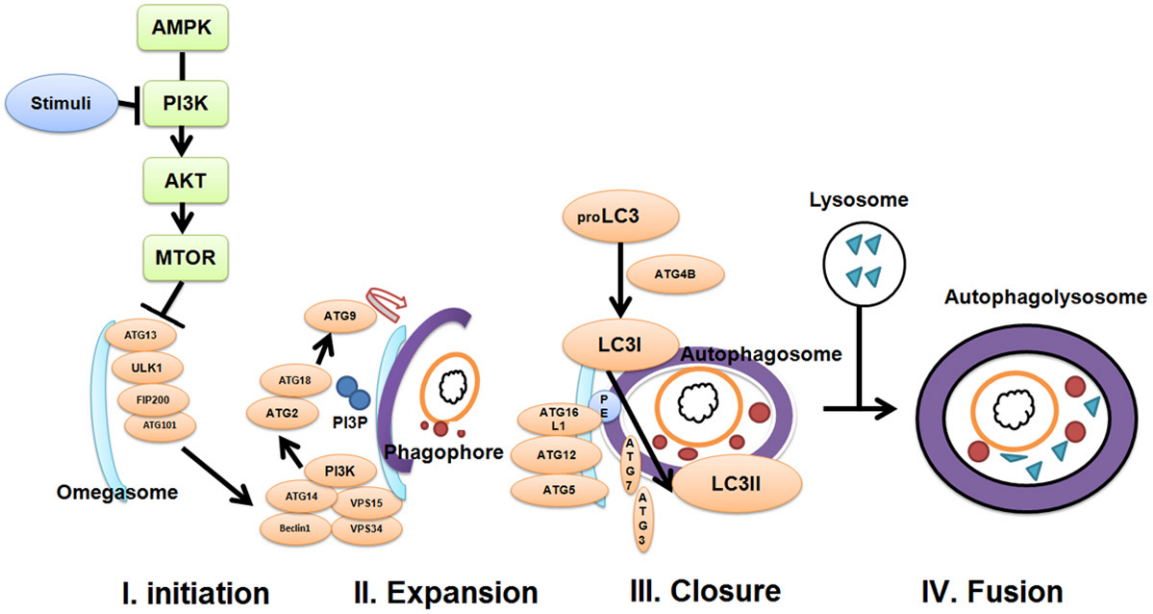

Figure 1. Four major stages of autophagosome formation in mammalian cells. I. Initiation. Different stimuli activate AMPK to prevent PI3K from phosphorylating its downstream target Akt, subsequently inhibiting mTOR and reducing the phosphorylation of ATG13. ATG13 interacts with ULK1, FIP 200 and ATG101 to form a ULK1 complex, which facilitates the induction of autophagy. II. Expansion. Activation of the ULK1 complex phosphorylates Beclin1, thereby enhancing the activity of Beclin1-ATG14-VPS34-VPS15-PI3K core complexes. The PI3K complex phosphorylates PI to generate PI3P, which is needed for the recruitment of the PI3P-binding protein ATG18 and its partner ATG2. These proteins are involved in ATG9 recycling. ATG4B cleaves the C-terminal 22 residues of the LC3 precursor (proLC3) to produce LC3-I. Following the interaction of ATG3 (E2-like enzyme) with the ATG16L1 complex (E3-ligase) and ATG7, LC3 is then conjugated to PE to produce LC3-PE (LC3-II). III. Closure. LC3-II specifically localizes to both the inner and outer autophagosomal membranes and remains on mature autophagosomes until they fuse with lysosomes. IV. Fusion. A mature autophagosome directly fuses to a lysosome or first fuses with an endosome before trafficking to the lysosome, forming an autophagolysosome.

mental animal studies supporting the hypotheses regarding the origin and roles of aberrant autophagy in EMS.

Autophagy

The word “autophagy” is derived from the Greek and means to eat (“phagy”) oneself (“auto”). As a non-apoptotic form of programmed cell death, autophagy is the major cellular pathway for the degradation of long-lived proteins and cytoplasmic organelles in eukaryotic cells [12, 13]. It is a constitutive catabolic pathway that mediates both nonspecific and targeted sequestration of cellular organelles and other macromolecules, permits the degradation of cellular components in lysosomes, and promotes the recycling of bioenergetic metabolites [14]. Extensive activation of autophagy is detrimental to the cell and results in autophagic cell death; conversely, a moderate autophagic response acts as a housekeeping and survival mechanism that contributes to maintaining cellular homeostasis under normal conditions or to overcoming stress-induced conditions caused by a large number of intracellular/extracellular stimuli, including hypoxia, a limited nutrient supply (e.g., amino acid starvation), oxidative stress, the invasion of microorganisms [15, 16], and certain forms of therapeutic stress (e.g., cytotoxic chemotherapy) [17]. For instance, autophagy has been shown to play an important role in promoting cell death by inducing caspases-dependent apoptosis in some normal cells and cancer cells [18-22]. Consequently, autophagy plays important roles in the process of cell growth, differentiation, tissue remodeling, cell immunity, environmental adaptation, and death [23, 24].

Autophagy is a ubiquitous physiological process that occurs in all eukaryotic cells [16]. Three primary types of autophagy have been reported: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) [25]. Autophagy commonly refers to macroau-

tophagy, because it is the most prevalent form of autophagy. Macroautophagy is a physiologically controlled, catabolic process by which cytoplasmic organelles and macromolecules are sequestered in autophagosomes (double-membrane vesicles that are derived from autophagosome precursors) and subsequently degraded after lysosomal fusion (autophagolysosomes that are derived from autophagosomes). The basic components resulting from lysosomal digestion are then reutilized for anabolic processes [13]. Four major stages of autophagosome formation have been characterized in both yeast and mammalian cells (**Figure 1**): initiation, expansion, closure, and fusion with the endolysosomal system [26]. The formation of a mature autophagosome plays a decisive role in the process of autophagy, which is regulated by a system of autophagy-related gene (ATG) products. The ATG proteins, which form six major groups, are recruited in a hierarchical manner to the pre-autophagosomal structure (PAS) in yeast or the omegasome in mammals. A double-track membrane, called the phagophore or isolation membrane, extends from the PAS to engulf cytoplasmic materials and organelles. The isolation membrane expands and then seals to form an autophagosome before it fuses with the vacuole in yeast or lysosome in mammals to release its contents for degradation [27].

The autophagy process is associated with numerous upstream signaling pathways and six major groups of ATG proteins. The most important signaling pathway is the class I Phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway [28]. The most upstream complex is the ATG1/ULK1 initiating complex, which contains the serine/threonine kinase ATG1/ULK1. In yeast, ATG1 forms a complex with ATG13, ATG17, ATG29, and ATG31 [29], whereas mammalian ULK1 complexes with ATG13, FIP200 (mammalian ATG17), and ATG101 [30]. Different stimuli activate AMP-dependent protein kinase (AMPK) and prevent PI3K from phosphorylating its downstream target Akt, thus inhibiting mTOR and subsequently reducing the phosphorylation of ATG13. ATG13 interacts with unc-51-like kinase 1 (ULK1), FIP 200 and ATG101 to form a ULK1 complex, which facilitates the induction of autophagy. When autophagy is induced, the initiating complex activates ATG1/ULK1 kinase activity and recruits downstream ATG complexes, including the multispanning transmembrane protein ATG9, followed by the autophagy-specific class III phosphatidylinositol 3-kinase (PI3K) complex [31]. Activation of the ULK1 complex phosphorylates Beclin1-regulated autophagy 1 (Ambra1), thereby enhancing the activity of Beclin1-ATG14-VPS34-VPS15 class III PI3K core complexes to promote autophagosome nucleation. The PI3K complex phosphorylates phosphatidylinositol (PI) at the hydroxyl group in the 3-position to generate phosphatidylinositol 3-phosphate (PI3P) at the PAS. PI3P is required for the recruitment of the PI3P-binding protein ATG18 (WIPI2 in mammals) and its partner ATG2, which are involved in ATG9 recycling [32]. Then, the subsequent expansion of the phagophore and the formation of the autophagosome require two complexes: the ATG16L1 complex (ATG12-ATG5-ATG16L1) and LC3-phosphatidyl ethanolamine (PE). The ATG12 system results in the formation of the ATG16/ATG12/ATG5 complex, which acts as an E3 ligase for the conjugation of ATG8 (LC3 in mammals) to phosphatidylethanolamine (PE) [33]. Although one ATG8 family member has been identified in yeast, mammals contain several homologues that form three subfamilies, including LC3, GABARAP, and GATE-16 [34]. Lipidation of LC3 is an important ubiquitin-like conjugation pathway. LC3 also recruits adaptor proteins such as p62 to autophagosomes, mediating the selective autophagy of cellular structures, protein aggregates and microorganisms. ATG4B cleaves the C-terminal 22 residues of the LC3 precursor (proLC3) to produce LC3-I. Following the interaction of ATG3 (E2-like enzyme) with the ATG16L1 complex (E3-ligase) and ATG7, LC3 is then conjugated to PE to produce LC3-PE (also called LC3-II). A mature autophagosome directly fuses to a lysosome or first fuses with an endosome before trafficking to the lysosome, forming an autolysosome. LC3-II specifically localizes to both the inner and outer autophagosomal membranes and remains on mature autophagosomes until they fuse with lysosomes to generate autolysosomes, after which the contents are then degraded by proteases, lipases, nucleases and glycosidases [35, 36].

Aberrant autophagy in EMS

In normal endometrial tissues, MAP1LC3A, which is widely used as an autophagic marker

Table 1. Autophagy levels in EECs and ESCs of normal endometrial tissues, eutopic endometrial tissues in patients with EMS and ectopic endometriotic tissues during the menstrual cycle

Tissues and cells		Proliferative phase		References	Secretory phase		References
		Early	Late		Early	Late	
Normal endometrial tissues	EECs	++	+++	[9] [39] [74]	++++	+++++	[9] [39] [74] [10] [11]
	ESCs	++	+++		+++	++++	
Eutopic endometrial tissues in patients with EMS	EECs	++		[10] [11]	/		/
	ESCs	++			+++		[10]
	Eutopic foci	++			+++		
Ectopic endometriotic tissues	EECs	++		[10] [11]	/		/
	ESCs	+			+		[39] [74] [10] [11]
	Ectopic foci	+			+		

+++++: The autophagy level in normal endometrial EECs in the late secretory phase.

and up-regulated during autophagy induction [37, 38], is expressed in endometrial glandular epithelial cells (EECs) and endometrial stromal cells (ESCs) throughout the menstrual cycle and is localized within the cytoplasm. In the early and late proliferative phases, MAP1LC3A staining in EECs and ESCs is negative or very weakly positive [9]. LC3-II expression increases during the late proliferative phase compared with the early proliferative phase, although the difference is not significant [39]. The ability of cells to undergo autophagy is reduced in the ectopic and eutopic endometrium of patients with EMS, and autophagy has been shown to be related to the pathogenesis and progression of EMS [40]. In eutopic EMS foci, a slightly decreased level of autophagy is identified in both proliferative EECs and ESCs compared with the endometrium from controls [10, 11]. In eutopic EMS tissues obtained from the secretory phase, autophagy in ESCs is still down-regulated compared to ESCs in the normal endometrium during the same phase. Regarding ectopic endometriotic tissues, Ruiz *et al.* [11] have identified a decrease in autophagy levels in EECs and ESCs; however, differences were observed among distinct endometriotic lesions (from ovaries, fallopian tubes, peritoneal, gastrointestinal, and skin). Ectopic EECs and ESCs in either proliferative or secretory phase are characterized by reduced autophagy compared with the normal endometrium; autophagy is very slightly reduced in the former (proliferative phase) and more significantly reduced in the latter (secretory phase). Moreover, the autophagy level in the secretory phase is further reduced in ectopic ESCs compared with eutopic ESCs [10].

As shown in **Table 1**, autophagy is primarily induced in human EECs during the secretory phase of the menstrual cycle [9, 11]. MAP1LC3A expression peaks in EECs during the late secretory phase [9]. Both the autophagosome number and LC3B expression are increased in secretory ESCs compared with proliferative ESCs, suggesting that the autophagy level is higher in secretory ESCs than in proliferative ESCs [10]. Accordingly, the induction of autophagy in endometrial cells treated with estrogen alone (as in the proliferative phase) increase with the addition of progesterone (as in the secretory phase) and simultaneously diversification is observed with the removal of estrogen and progesterone (as in the menstrual phase) [39]. In contrast, another study has recently found that the autophagy level (detecting LC3B) is reduced in the secretory phase compared with the proliferative phase in both human EECs and the ESCs of controls, possibly because of the small sample size or the limitations of the immunohistochemical staining technique, which require further study [11]. Similar to normal ESCs, the autophagy level is higher in eutopic ESCs in the secretory phase than in eutopic ESCs in the proliferative phase of the menstrual cycle from patients with EMS [10]. However, a similar change in the endometriotic tissue-derived ESCs is not observed during the menstrual cycle, which maintains a nearly constant autophagy level throughout the menstrual cycle [10]. Similarly, cycle-dependent

induction of endometrial cell autophagy in the ectopic endometrium of patients with EMS is described by Choi *et al.* [39]. A constant level of autophagy induction is detected throughout the menstrual cycle in ovarian endometriotic cysts, which is mediated by the disinhibition of mTOR activity and is related to decreased apoptosis. Based on these findings, the low level of autophagy observed in secretory phase ESCs is involved in the pathogenesis of EMS. Accordingly, ESCs are primarily involved in the interaction between the endometrial tissue and the mesothelial cell lining of the peritoneum and play a fundamental role in the pathogenesis of EMS [41].

Generally, the level of autophagy in ectopic foci (actually in both the ectopic and eutopic endometrium of patients with EMS) is decreased (**Table 1**). Nevertheless, Allavena *et al.* have reported a significant up-regulation of autophagy in ovarian endometriomas compared with the eutopic endometrium of patients with EMS or healthy women [42]. Moreover, a significant increase in LC3B expression in the epithelium of fallopian tube and ovarian endometriotic lesions has recently been observed compared with the epithelium from the secretory endometrium of controls [11]. On one hand, endometriotic cells inside the ovarian endometriotic cysts experience a persistent condition of oxidative stress with high levels of free redox-active iron that retrospectively act as an autophagic stimulus, which has been confirmed by the notably up-regulated expression level of HO-1 [42], the rate-limiting enzyme in heme degradation that is induced by high levels of oxidative stress and inflammation [43]. On the other hand, a dramatic loss of the master inducer of apoptosis and negative regulator of cell proliferation, p53 [44], has been observed in ovarian endometriotic cyst tissues, which in addition to suggesting that apoptosis is impaired, may also be responsible for stimulating autophagy [42]. Low cytosolic levels of p53 obtained through pharmacologic inhibition or genetic depletion/deletion trigger autophagy [45], likely by inducing the derepression of the autophagy-initiating ULK1 complex [46]. According to a more recent study, the expression of HIF-1α (hypoxia-inducible factor-1α), a heterodimeric transcriptional factor mediating the cellular response to hypoxia, is increased in ovarian endometriotic lesions and enhances the migration and invasion of HESCs by upregulating autophagy in a hypoxic environment. Thus, autophagy is also induced through HIF-dependent pathways, which are involved in the high autophagy level detected in ovarian endometriotic lesions [47].

Autophagy-related genes (ATGs) in EMS

Autophagy is a catabolic process with complex regulatory mechanisms that has been highly conserved throughout biological evolution. Currently, more than 30 species of autophagy-related genes (ATGs) and multiple cellular pathways have been shown to be involved in autophagy [48]. The formation of autophagosomes requires a number of components called autophagy-related proteins, which are regulated through the autophagy pathway [49]. Gene expression is altered in eutopic endometria from patients with EMS compared with controls [50]. Retrospectively, autophagy is down-regulated in both the ectopic (lower) and eutopic endometrium of patients with EMS, with the exception of the ovarian endometriotic tissues. Accordingly, differences in ATG expression have been detected between eutopic and ectopic ESCs as well as between these cells and control ESCs [10]. Furthermore, the mRNA and protein levels of markers of autophagy are further down-regulated in the ectopic murine endometrium compared with the eutopic murine endometrium [11].

As shown in our previous work, the genes involved in autophagic vacuole formation or regulators of autophagy and apoptosis, such as *SNCA*, *RGS19*, *IGF1*, *ATG9B*, *ATG12*, *ATG10*, *IFNG*, *PIK3CG*, and *DAPK1*, are also decreased in eutopic secretory human ESCs compared with normal ESCs [10]. The expression of genes associated with autophagy initiation and regulation, such as *p62*, *CXCR4*, *ESR1*, and *mTOR*, is up-regulated and *LC3-II* and *BECN1* expression are down-regulated in ectopic ESCs compared with eutopic ESCs [10]. More recently, Ruiz *et al.* have established a mouse model of EMS and obtained the similar results. Upon the induction of EMS in the murine eutopic endometrium, the RNA levels of 13 markers of autophagy in uterine horns (the phase in the menstrual cycle was not specified) are dysregulated, including 12 markers (*ATG4C*, *ATG9B*, *BNIP3*, *IRGM1*, *EIF2AK3*, *FAS*, *LC3A*, *LC3B*, *GABARAPL1*, *PTEN*, *SQSTM1* and *PRKAA1*) with significantly decreased expression and a remarkable increase in *IGF1* expression, com-

Table 2. Several representative autophagy-related genes (*BECN1, LC3, p62* and *CXCR4*) in eutopic and ectopic ESCs of EMS. Their autophagy-related functions and their dysregulation associated with the pathogenesis of EMS are presented

ATG	Autophagy-related Function	Eutopic ESCs	Ectopic ESCs	Relation to EMS
BECN1	Autophagy promoting gene; Vesicle nucleation during autophagosome formation; Forming a complex with UVRAG to regulate PIK3C3; Interaction with the Bcl-2.	↓	↓	Negatively correlated with serum CA125 and pelvic pain in EMS.
LC3	Autophagy induction gene; Converting from LC3-I to LC3-II; LC3-II located in autophagosome membrane.	↓	↓	Down-regulation of autophagosomes in eutopic or ectopic ESCs.
p62	Autophage adapting gene; Binding ubiquitinated cargo for degradation; Regulating autophagy to target designated cargo.	↑/↓	↑/↓	Autophagy dysregulation in EMS.
CXCR4	Candidate autophagy-related gene; Suppressing basal autophagy in a mTORC1-independent fashion.	↑	↑	Estrogen-driven CXCL12/CXCR4 expression to repress autophagy in ESCs.

↑: up-regulation; ↓: down-regulation.

pared with controls (non-induced) [11]. RNA levels of markers of autophagy, including *ATG5*, *ATG4B*, *ATG2B*, *ATG7*, *BECN1, p62*, *GABARAPL1-I*, *LC3B-I*, *LC3B-II*, *LC3A-I*, and *LC3A-II*, are significantly decreased in endometriotic lesions compared with the uterine horns of PBS-treated mice. In addition, the authors have noted a significant increase in the expression of the p21 protein, a cyclin-dependent kinase inhibitor involved in cell cycle arrest that attenuates the viability of cells transfected with the *ATG7* siRNA. Thus, the reduction in cell viability is proposed to have occurred through a similar noncanonical autophagy mechanism or independently of autophagy; however, further studies are required to elucidate the mechanism [11]. Specifically, the differences in the examined species, specimens and phases of menstrual cycle in these two studies may have contributed to the distinct changes in *IRGM1* expression between eutopic EMS tissues and the normal endometrium. Therefore, further study is warranted.

In particular, an increasing number of studies have recently focused on several representative ATGs (**Table 2**). *BECN1*, the product of autophagy promoting gene (*ATG6*), is required for vesicle nucleation during autophagosome formation, forms a complex with UVRAG to regulate *PIK3C3*, and is an important convergence point between autophagy and apoptosis because it interacts with the anti-apoptotic and anti-autophagic protein Bcl-2 [51, 52]. Autophagy defects caused by loss of *BECN1* may be associated with the malignant phenotype and a poor prognosis for patients with ovarian clear cell carcinomas [53]. *BECN1 mRNA and Beclin-1 protein* expression are significantly decreased in both eutopic and ectopic endometriotic tissues and are negatively correlated with serum CA125 levels and pelvic pain, which may facilitate the invasion of the endometrial stroma and glands into the myometrium and the diffusive process of adenomyosis in the myometrium, subsequently contributing to the pathogenesis and progression of EMS [40, 54].

During the induction of autophagy, microtubule-associated protein light chain 3 (LC3) is converted from LC3-I to LC3-II, and then LC3-II localizes to isolated membranes and autophagosomes [49, 55]. Accordingly, LC3A-I, LC3A-II, LC3B-I and LC3B-II tend to be down-regulated in eutopic and ectopic endometriotic tissues. The adaptor molecule p62 (which binds ubiquitinated cargo for degradation) enables the autophagy pathway to selectively target designated cargo to isolated, nascent LC3-positive membranes, leading to rapid acidification and enhanced killing of the ingested organism. The p62 protein is up-regulated in cells with autophagy defects [56]. As shown in our previous studies, secretory phase eutopic and endometriotic tissues and ESCs are characterized by the down-regulation of autophagosomes, decreased conversion of LC3-I to II, reduced *BECN1* expression and elevated *p62* and *CXCR4* expression compared with the normal endometrium and ESCs. Additionally, the change in ectopic ESCs is even more intense. We have also defined *CXCR4* as a candidate ATG in the EMS-derived ESCs [10]. In contrast,

the expression of the LC3-II protein is increased and the expression of the p62 protein is decreased in patients with ovarian endometriomas compared with patients with eutopic endometria or disease-free participants [42]. Interestingly, an independent report has postulated that the levels of LC3B, which is predominantly expressed in and localized to the epithelium compared to the stromal components, are increased in ectopic endometria of EMS-induced mice compared with eutopic endometria of controls, which may be associated with an accumulation of lipid droplets in the epithelial cells, but further work is necessary to understand the clinical implications of this finding [11].

The role of autophagy in EMS

Autophagy and the regulation of ESC proliferation

EMS is increasingly being recognized as a condition in which ectopic endometrial cells exhibit abnormal regulation of proliferation and apoptosis in response to appropriate stimuli [57]. The PI3K/Akt/mTOR signal transduction pathway, the core regulatory pathway related to autophagy, has been widely studied in breast cancer, endometrial cancer, bladder cancer, and other malignant tumors [58]. Akt up-regulation, along with mTOR up-regulation, is also observed in EMS and is expected to impair the autophagic response in endometriotic tissues [59, 60] and promote the survival of endometriotic cells [61]. According to the study by Leconte *et al.*, the rate of endometrial cell proliferation is significantly decreased in mice with EMS that are treated with inhibitors of the PI3K/Akt/mTOR pathway that act on the deep infiltrating EMS uterus [62]. Moreover, suppression of autophagy by CXCL12 promotes the growth and proliferation of ESCs *in vitro* [10].

Autophagy and the regulation of ESC apoptosis

As reported by Chang *et al.*, EMS is associated with p53, a tumor suppressor protein that negatively regulates cell proliferation and induces apoptotic cell death [44, 63]. In addition, the levels of Bcl-2, an oncoprotein that inhibits apoptotic cell death [64], differ in different phases of the menstrual cycle and in endometriotic lesions at different sites [57]. Based on the findings from these studies, apoptosis plays a major role in the pathophysiology of EMS. Rather than being two independent events, autophagy and apoptosis are two cross-talking mechanisms [65], and autophagy facilitates the engulfment and lysosomal degradation of apoptotic bodies [66]. Autophagy has also been shown to exert a proapoptotic effect on human endometrial cells because the accumulation of autophagosomes promotes apoptosis through an increase in the Bax: Bcl-2 ratio, followed by caspase activation in endometrial Ishikawa cells; the induction of autophagy also plays a key role in regulating endometrial cell apoptosis during the human endometrial cycle [9]. According to several subsequent studies, alterations in the induction of autophagy induced by aberrant mTOR activity may contribute to abnormal apoptosis in EMS, and the induction of autophagy induced by mTOR inhibition is closely related to the induction of apoptosis in both endometrial and endometriotic cells [39]. Moreover, a recent study has concluded that a decrease in autophagic activity in ectopic and eutopic endometrial cells leads to a reduction in autophagy-dependent degradation of proteins and programmed cell death [67].

Autophagy and the crosstalk between ESCs and NK cells

Autophagy has been shown to play a role in antigen presentation [68], and the inhibition of autophagy may allow endometrial cells to escape from immune surveillance and facilitate intramyometrial implantation [54] and EMS. Similarly, autophagy is associated with IL-15 and possibly indirectly influences NK cell differentiation. As shown in our recent study, abnormally high levels of IL-15 in the ectopic endometrium not only directly stimulate the proliferation and invasion and restrict the apoptosis in ESCs in an autocrine manner but also decrease the killing activity of the NK cells in a paracrine manner, which may further contribute to the immune escape of ESCs, ultimately promoting the ectopic growth and implantation of ESCs within the peritoneal cavity [67]. The decrease in ESC autophagy in subjects with EMS may enhance the reactivity of ESCs to IL-15 by increasing the expression of IL-15 receptors and amplifying the role of IL-15 in the dialogue between ESCs and NK cells [67]. Moreover, ESCs restrict NK cell differentiation within the abdominal cavity and may partici-

pate in the induction and maintenance of phenotypes and functions of the NK cells and influence the level of inflammation in the endometriotic milieu. The phenotypes and functions of the NK cells in the endometriotic milieu may be involved in the dysregulated autophagy of ESCs, which requires additional research [67].

Moreover, autophagy may be involved in EMS through the CXCR4-CXCL12 axis, which has also been shown to have both immune (lymphocyte chemotaxis) and non-immune functions. The CXCR4-CXCL12 axis has roles in tissue repair, angiogenesis, invasion and migration in EMS, inhibits sex hormone-regulated autophagy, and leads to the anomalous growth of endometrial cells at the ectopic sites in EMS [10, 69]. CXCL12/CXCR4 signaling at the maternal-fetal interface is involved in recruiting NK cells from peripheral blood (pNK) to the decidua during early pregnancy, further inducing pNK to differentiate into decidual NK cells, which promotes the formation of the maternal-fetal interface and the establishment and maintenance of a normal pregnancy [70-72]. Therefore, estrogen-CXCL12/CXCR4 signaling not only directly inhibits ESC autophagy but also recruits more pNK cells to the microenvironment of an ectopic lesion, regulating the function of these NK cells, promoting the immune escape of ESCs, and ultimately accelerating the development of EMS.

Autophagy and other regulatory effects on ESCs

As autophagy-associated pathways, MAPK/ERK and PI3K/Akt/mTOR signaling have been shown to be involved in the adhesion of endometrial cells promoted by cell adhesion molecules (CAM) in EMS, the regulation of the degradation and anabolism of extracellular matrix (ECM) through matrix metalloproteinase (MMP)/tissue inhibitors of matrix metalloproteinase (TIMP) and the regulation of the expression of vascular endothelial growth factor (VEGF). The activation of these previously mentioned pathways down-regulates ESC autophagy and promotes the degradation of the ECM and the formation of new blood vessels, ultimately facilitating the transition, adhesion, invasion and survival of the ectopic endometrium in EMS [73]. In contrast, autophagy is significantly up-regulated in patients with ovarian endometriomas compared with the eutopic endometria of affected or healthy women, which is regarded as a further adaptive mechanism that contributes to the reduced susceptibility to apoptotic cell death, the survival of endometrial cells in ectopic sites, and lesion maintenance from a pathophysiologic perspective [42, 57].

Factors involved in regulating the autophagy level in ectopic foci

Hormones

In the human endometrium, two central balancing factors, estrogen and progestogen, control autophagy in endometrial Ishikawa cells during the menstrual cycle. Ishikawa cells are typically cultured in the presence of both hormones, and an increased degree of autophagy and a higher incidence of apoptotic cell death is observed upon the withdrawal of one or both hormones [9, 39]. Hormone deprivation and acute inflammation are identified as two potent inducers of autophagy in the mouse uterus. As the uterus exhibits an acute inflammatory response to incoming semen, the activation of autophagy in the uterine stroma in the first days of pregnancy is attributed to the effects of inflammation. The mouse ovariectomy (OVX) model is used to monitor the effects of individual steroid hormones on autophagy. In response to hormone deprivation after OVX, the uterus shows the highest levels of autophagy, as indicated by the higher expression levels of LC3-II and ATG5 proteins. After OVX, autophagy is activated in all major uterine cell populations, which differs from the more localized autophagy pattern observed on day 1 of pregnancy. When either 17β estradiol (E2) or progesterone (P4) is administered, the levels of LC3-II and ATG5 decrease as early as 2 h after hormone administration. Beclin1 represents a distinct expression profile, suggesting that it is regulated by a different mechanism [74]. In the uterus, mammalian target of rapamycin (mTOR) is currently considered a key player in mediating the effects of hormones on autophagy. mTOR itself is an estrogen-responsive factor that strongly inhibits autophagy [75].

The typical characteristics of EMS are increased production of estradiol, which stimulates the proliferation of endometriotic tissues, and perturbations in the progesterone response, which is known as progesterone resistance [76-78].

Estrogen and progestogen modulate apoptosis in human endometrium and endometriotic cells and tissues and further contribute to the incidence and development of EMS [79]. Endometriotic cells have been shown to respond abnormally to ovarian steroids, which contributes to the dysregulation of autophagy in these cells [39]. Cornillie *et al*. [80] have described an increase in lysosomal autophagy after endometriotic implants are administered an antiprogesterone treatment. However, low progesterone has recently been suggested to be associated with decreased autophagy in the ectopic foci of patients with EMS, as dienogest treatment of endometriotic cells suppresses AKT and ERK1/2 activity, thereby inhibiting mTOR, inducing autophagy, and promoting apoptosis, possibly through progestogenic actions [81]. EMS appears to contain an altered complement of steroid hormone receptors compared with the normal endometrium. Estrogen receptor α (ERα) is significantly up-regulated, whereas progesterone receptor (PR) is down-regulated in eutopic and ectopic (more significantly) ESCs. ERα up-regulation and an enhancement of estrogen function repress ESC autophagy by up-regulating CXCL12/CXCR4 signaling to further promote ESC growth [10]. In contrast, progestogen inhibits the effect of estrogen on ESC autophagy [10]. Thus, estrogen seems to negatively regulate autophagy in the human endometrium through a novel chemokine-mediated mechanism. However, the regulatory axis that involves CXCL12 seems to be mTOR-independent [82]. Moreover, the production of IL-15, which regulates the proliferation, apoptosis, and invasion of ESCs in vitro, is regulated by ovarian steroid hormones in normal human endometrial cells. A decrease in ESC autophagy promotes the expression of IL-15 receptors, increases the sensitivity of ESCs to IL-15, and improves the stimulatory effect of IL-15 on ESCs [67, 83]. Therefore, ovarian steroid hormones may regulate IL-15 production through effects on ESC autophagy and the subsequent growth and invasion of ESCs.

Drugs

Hydroxychloroquine (HCQ), an autophagic flux inhibitor used to treat malaria and inflammatory and autoimmune diseases [84], is considered a lysosomotropic agent because it increases the pH of acidic compartments and inhibits the fusion of the autophagosome with the lysosome [85-87]. As shown in the study by Ruiz *et al*., the levels of autophagic markers in human endometriotic cells and human ESCs increase following HCQ treatment, suggesting that the use of HCQ (or an inhibitor targeting specific autophagic mediator) may be detrimental to both human endometrial and endometriotic cell survival *in vitro*. The drug also appears to have an effect on lesion histopathology (the absence of glandular components) and lesion numbers, but not on lesion size. Additionally, HCQ increases the number of macrophages and the levels of the IP-10 chemokine within the peritoneal cavity of a mouse model of EMS [11].

Rapamycin, a specific mTOR inhibitor [88], induces autophagy in all mammalian cell types tested to date [89]. According to Choi *et al*., rapamycin induces autophagy and promotes apoptosis. However, the pro-apoptotic effect of rapamycin is reversed by an autophagy inhibitor, 3-MA. Thus, mTOR inhibition promotes endometriotic cell apoptosis by inducing autophagy [39]. Moreover, rapamycin significantly inhibits the expression of the IL-15 receptor, an autophagy inhibitor [67].

Mullerian inhibiting substance (MIS), a 140-kDa homodimer glycoprotein and a member of the TGF-β superfamily of biological response modifiers, causes Mullerian ducts to regress in developing male embryos [90]. According to the study by Renaud *et al*., both the normal human endometrium and endometrial cancers express the MIS receptor, and MIS inhibits the proliferation of a number of human endometrial cancer cell lines [91]. As shown in the study by Borahay *et al.* [92], MIS treatment induces autophagy in endometriotic cells by inducing Beclin-1 and ERK activity. The MIS treatment also inhibits the proliferation and induces the apoptosis of ectopic endometrial cell lines.

The GnRH-II antagonist trptorelix-1 has been shown to induce autophagy in prostate cancer cells [93]. A GnRH-II antagonist has recently been shown to exert a significantly stronger anti-proliferative effect on breast, ovarian, and endometrial cancer cells than the GnRH-I agonist triptorelin [94]. Therefore, Ren *et al.* propose that GnRH-II antagonists might hold promise in the treatment of adenomyosis as autophagy inducers [53], as well as in the treatment in EMS, which requires further study.

Bafilomycin A1 (Baf A1), a chemical inhibitor of V-ATPase, is commonly used to block autophagosome-lysosome fusion in mammalian cell culture studies, causing an accumulation of autophagosomes upon autophagy induction that is independent of its effect on lysosomal pH, possibly through a Ca^{2+}-dependent mechanism [95-97]. A study has concluded that the rates of cell death and apoptosis in Baf A1-treated Ishikawa cells are significantly higher than in Ishikawa cells treated with 3-MA, suggesting that a certain level of autophagosome accumulation may be needed to promote endometrial cell death and apoptosis [9]. Similarly, the Baf A1 treatment may influence the autophagy level of eutopic and ectopic foci in EMS by causing an accumulation of autophagosomes and subsequently promoting cell death and apoptosis, which still requires further study.

Hypoxia and oxidative stress

Autophagy acts as a spontaneous pro-survival mechanism in cells under hypoxia and oxidative stress [13]. Hypoxia is a well-known inducer of autophagy [98]. Based on accumulating evidence, hypoxia may play a role in the survival and angiogenesis of ectopic endometrial cells [99-101], which is likely associated with hypoxia-responsive miRNAs, such as miR-20a and miR-199a [102, 103]. Xu *et al.* identified higher levels of miR-210 expression in endometriotic cells grown in a hypoxic environment, which may contribute to the pathological development of EMS by reducing the apoptosis of endometriotic cells, enhancing cell survival and promoting autophagy through a Bcl-2/Beclin-1 pathway [104]. Autophagy induction in ectopic foci would be facilitated by regional oxidative stress. Because of the cyclic bleeding in endometriotic tissues, the hemoglobin released during hemolysis leads to the accumulation of high levels of heme. Heme undergoes heme oxygenase-catalyzed degradation into biliverdin, carbon monoxide, and iron [105]. Oxidative stress has been reported to promote the induction of autophagy in patients with ovarian EMS compared with the eutopic endometria of affected or healthy women, because a significant increase in the levels of the heme oxygenase-1 (HO-1) protein has been detected in endometriomas [42].

Other related factors

In many cell types, autophagy is negatively regulated by the PI3K/AKT and MEK1/2-ERK1/2 pathways, both of which activate mTOR, the major negative regulator of autophagy [89, 106]. Interestingly, endometriotic lesions have been shown to exhibit enhanced activation of AKT, ERK1/2, and mTOR compared with the normal endometrium, suggesting that inappropriate activation of AKT and ERK1/2 may lead to increased mTOR activity and the subsequent inhibition of autophagy in endometriotic tissue [107-109]. Accordingly, mTOR activity is abnormally increased in endometriotic lesions compared with the normal eutopic endometrium [59, 110]. Moreover, aberrant mTOR activity in ovarian endometriotic cysts leads to alterations in endometrial cell autophagy, which are associated with abnormal apoptosis, and mTOR inhibition promotes endometriotic cell apoptosis by inducing autophagy [39]. CXCL12 mainly inhibits autophagy by down-regulating autophagosomes and the conversion of LC3B-I to LC3B-II, reducing Beclin-1 expression and increasing p62 levels; these activities of CXCL12 are partially dependent on the NF-kB signaling pathway. The abnormally high level of CXCL12/CXCR4 expression may promote the survival and growth of ESCs in the endometriotic milieu by restricting secretory phase ESC autophagy [10]. Retrospectively, in endometriotic cells, miR-210 promotes autophagy in response to hypoxia, contributing to the enhanced survival of hypoxic endometriotic cells [104]. An HCQ treatment increases the levels of IP-10 in the peritoneal cavity in a mouse model of EMS, which may have created an unfavorable environment for lesion development. However, further studies are required to determine whether IP-10 modulates the autophagic pathway [11].

Summary

Autophagy is accepted to play important roles in the development and treatment of cancers. In recent years, accumulating studies have focused on the effect of altered autophagy on EMS. As shown in **Figure 2** and **Figure 3**, the level of autophagy in both ectopic stromal and epithelial cells decreases in ectopic foci from patients with EMS, particularly during the secretory phase of the menstrual cycle, which is regulated by hormones, hypoxia, oxidative stress, and many other related factors, leading

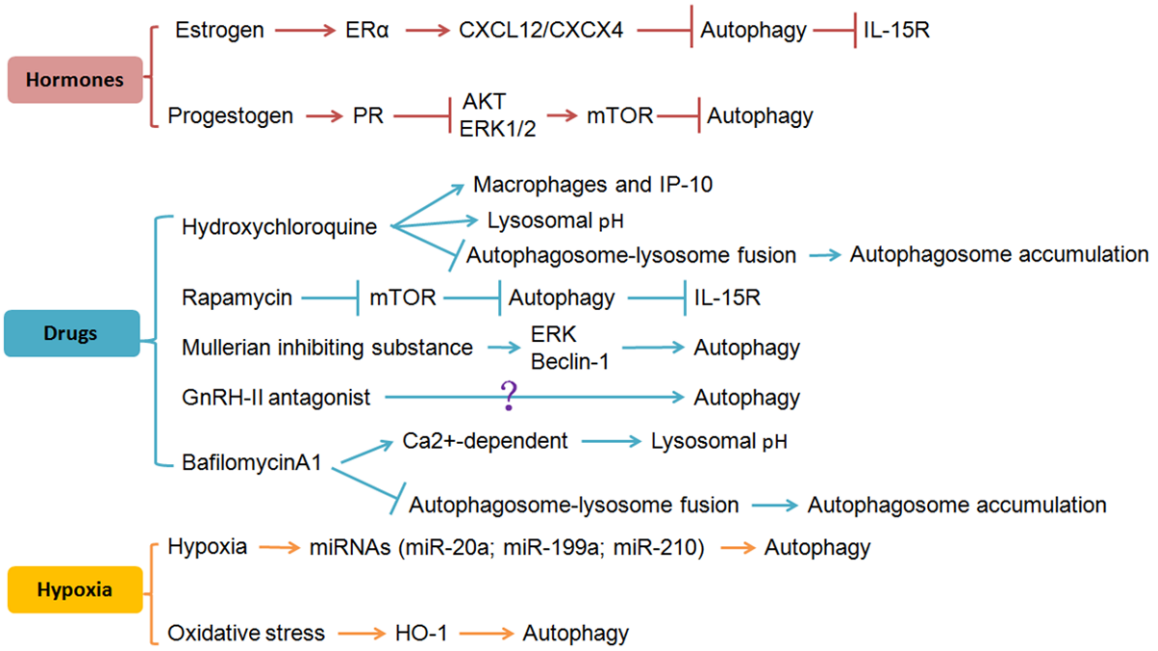

Figure 2. Factors involved in regulating the autophagy level in ectopic foci. Female hormones (estrogen and progestogen), several drugs (hydoxychloroquine, rapamycin, mullerian inhibiting substance, GnRH-II antagonist, and bafilomycin A1), hypoxia and oxidative stress are reported to affect the dysregulated autophagy level in EMS via different mechanisms or pathways.

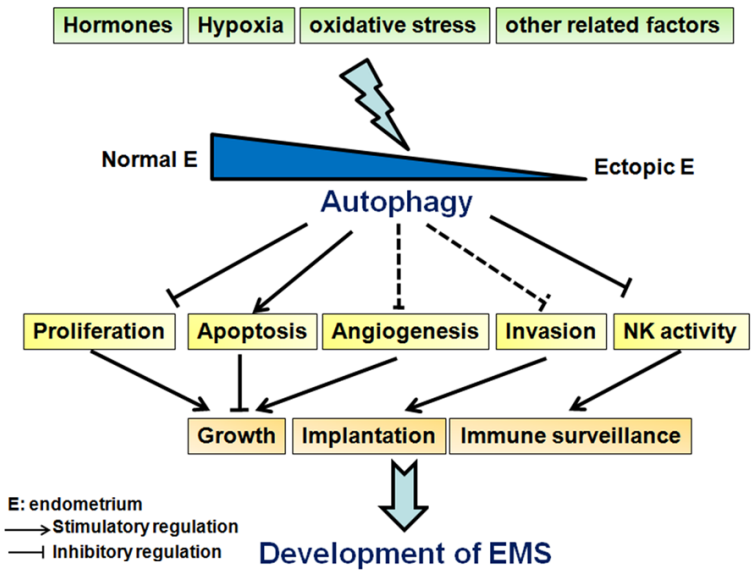

Figure 3. The role of autophagy in the progression of endometriosis. Hormones, hypoxia, oxidative stress, and many other related factors significantly decrease autophagy in the ectopic endometrium, resulting in increased proliferation, invasion and angiogenesis, and decreased apoptosis and NK activity in ectopic foci that ultimately contributes to the occurrence and development of EMS.

to increased proliferation and decreased apoptosis of ectopic foci through downstream molecules and finally contributing to the occurrence and development of EMS. Based on these results, autophagy is decreased in endometriotic cells, which is probably a significant mechanism in EMS. The mRNA and protein levels of the currently known markers of autophagy are further down-regulated and important signal transduction pathways involved in autophagy are altered in ectopic tissues. Thus, fundamental and clinical studies are now focusing on new therapeutic strategies for EMS aimed at autophagic markers or pathways. Additionally, some drugs (**Figure 2**), such as dienogest and HCQ, have been verified to exert a therapeutic effect on EMS by promoting the autophagy of ectopic tissues. Therefore, strategies that adjust the level of autophagy in ectopic foci may be a potential target in the clinical treatment of EMS, and fur-

ther studies are necessary to identify and evaluate this new, latent therapy.

Acknowledgements

This study was supported by grants from the Major Research Program of the National Natural Science Foundation of China (NSFC) (No. 91542108, No. 81471513, and No. 31671200), the Shanghai Rising-Star Program (16QA1400800), the Development Fund of Shanghai Talents (201557), the Oriented Project of Science and Technology Innovation from Key Lab. of Reproduction Regulation of NPFPC (CX2017-2), the Program for Zhuoxue of Fudan University (all to MQL), the NSFC (No. 81601354), the National Science Foundation of Jiangsu Province (No. BK20160128), and the Fundamental Research Funds for the Central Universities (No. 021414380180) (to JM) and the NSFC (No. 31600735) (to KKC).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ming-Qing Li, Laboratory for Reproductive Immunology, Hospital of Obstetrics and Gynecology, Fudan University, Zhao Zhou Road 413, Shanghai 200011, People's Republic of China. Tel: 86-21-63457331; Fax: 86-21-63457331; E-mail: mqli@fudan.edu.cn

References

[1] Eskenazi B and Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am 1997; 24: 235-258.

[2] Pritts EA and Taylor RN. An evidence-based evaluation of endometriosis-associated infertility. Endocrinol Metab Clin North Am 2003; 32: 653-667.

[3] Bulun SE. Endometriosis. N Engl J Med 2009; 360: 268-279.

[4] Giudice LC and Kao LC. Endometriosis. Lancet 2004; 364: 1789-1799.

[5] Frackiewicz EJ. Endometriosis: an overview of the disease and its treatment. J Am Pharm Assoc (Wash) 2000; 40: 645-657; quiz 699-702.

[6] Griffith JS, Liu YG, Tekmal RR, Binkley PA, Holden AE and Schenken RS. Menstrual endometrial cells from women with endometriosis demonstrate increased adherence to peritoneal cells and increased expression of CD44 splice variants. Fertil Steril 2010; 93: 1745-1749.

[7] Figueira PG, Abrao MS, Krikun G and Taylor HS. Stem cells in endometrium and their role in the pathogenesis of endometriosis. Ann N Y Acad Sci 2011; 1221: 10-17.

[8] Goumenou AG, Matalliotakis IM, Tzardi M, Fragouli YG, Mahutte NG and Arici A. Apoptosis and differential expression of apoptosis-related proteins in endometriotic glandular and stromal cells. J Soc Gynecol Investig 2004; 11: 318-322.

[9] Choi J, Jo M, Lee E, Oh YK and Choi D. The role of autophagy in human endometrium. Biol Reprod 2012; 86: 70.

[10] Mei J, Zhu XY, Jin LP, Duan ZL, Li DJ and Li MQ. Estrogen promotes the survival of human secretory phase endometrial stromal cells via CXCL12/CXCR4 up-regulation-mediated autophagy inhibition. Hum Reprod 2015; 30: 1677-1689.

[11] Ruiz A, Rockfield S, Taran N, Haller E, Engelman RW, Flores I, Panina-Bordignon P and Nanjundan M. Effect of hydroxychloroquine and characterization of autophagy in a mouse model of endometriosis. Cell Death Dis 2016; 7: e2059.

[12] Klionsky DJ and Emr SD. Autophagy as a regulated pathway of cellular degradation. Science 2000; 290: 1717-1721.

[13] Levine B and Klionsky DJ. Development by self-digestion: molecular mechanisms and biological functions of autophagy. Dev Cell 2004; 6: 463-477.

[14] He C and Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet 2009; 43: 67-93.

[15] Mizushima N, Levine B, Cuervo AM and Klionsky DJ. Autophagy fights disease through cellular self-digestion. Nature 2008; 451: 1069-1075.

[16] Yang YP, Liang ZQ, Gu ZL and Qin ZH. Molecular mechanism and regulation of autophagy. Acta Pharmacol Sin 2005; 26: 1421-1434.

[17] Sun Y, Liu JH, Jin L, Pan L, Sui YX, Yang Y and Shi H. Beclin 1 influences cisplatin-induced apoptosis in cervical cancer CaSki cells by mitochondrial dependent pathway. Int J Gynecol Cancer 2012; 22: 1118-1124.

[18] Boya P, Gonzalez-Polo RA, Casares N, Perfettini JL, Dessen P, Larochette N, Metivier D, Meley D, Souquere S, Yoshimori T, Pierron G, Codogno P and Kroemer G. Inhibition of macroautophagy triggers apoptosis. Mol Cell Biol 2005; 25: 1025-1040.

[19] Boya P, Gonzalez-Polo RA, Poncet D, Andreau K, Vieira HL, Roumier T, Perfettini JL and Kroemer G. Mitochondrial membrane permeabilization is a critical step of lysosome-initiated apoptosis induced by hydroxychloroquine. Oncogene 2003; 22: 3927-3936.

[20] Choi J, Jo M, Lee E and Choi D. The role of autophagy in corpus luteum regression in the rat. Biol Reprod 2011; 85: 465-472.
[21] Choi J, Jo M, Lee E and Choi D. Induction of apoptotic cell death via accumulation of autophagosomes in rat granulosa cells. Fertil Steril 2011; 95: 1482-1486.
[22] Wu YC, Wu WK, Li Y, Yu L, Li ZJ, Wong CC, Li HT, Sung JJ and Cho CH. Inhibition of macroautophagy by bafilomycin A1 lowers proliferation and induces apoptosis in colon cancer cells. Biochem Biophys Res Commun 2009; 382: 451-456.
[23] Klionsky DJ. Autophagy. Curr Biol 2005; 15: R282-283.
[24] Lockshin RA and Zakeri Z. Apoptosis, autophagy, and more. Int J Biochem Cell Biol 2004; 36: 2405-2419.
[25] Massey AC, Zhang C and Cuervo AM. Chaperone-mediated autophagy in aging and disease. Curr Top Dev Biol 2006; 73: 205-235.
[26] Lamb CA, Yoshimori T, Tooze SA. The autophagosome: origins unknown, biogenesis complex. Nat Rev Mol Cell Biol 2013; 14: 759-774.
[27] Davis S, Wang J and Ferro-Novick S. Crosstalk between the secretory and autophagy pathways regulates autophagosome formation. Developmental Cell 2017; 41: 23-32.
[28] Dunlop EA and Tee AR. mTOR and autophagy: a dynamic relationship governed by nutrients and energy. Semin Cell Dev Biol 2014; 36: 121-129.
[29] Ragusa MJ, Stanley RE and Hurley JH. Architecture of the Atg17 complex as a scaffold for autophagosome biogenesis. Cell 2012; 151: 1501-1512.
[30] Qi SQ, Kim DJ, Stjepanovic G and Hurley JH. Structure of the human Atg13-Atg101 HORMA heterodimer: an interaction hub within the ULK1 complex. Structure 2015; 23: 1848-1857.
[31] Rao Y, Perna MG, Hofmann B, Beier V and Wollert T. The Atg1-kinase complex tethers Atg9-vesicles to initiate autophagy. Nat Commun 2016; 7: 10338.
[32] Obara K, Sekito T, Niimi K and Ohsumi Y. The Atg18-Atg2 complex is recruited to autophagic membranes via phosphatidylinositol 3-phosphate and exerts an essential function. J Biol Chem 2008; 283: 23972-23980.
[33] Noda NN, Fujioka Y, Hanada T, Ohsumi Y and Inagaki F. Structure of the Atg12-Atg5 conjugate reveals a platform for stimulating Atg8-PE conjugation. EMBO Rep 2013; 14: 206-211.
[34] Slobodkin MR and Elazar Z. The Atg8 family: multifunctional ubiquitin-like key regulators of autophagy. Essays Biochem 2013; 55: 51-64.
[35] Maycotte P and Thorburn A. Targeting autophagy in breast cancer. World J Clin Oncol 2014; 5: 224-240.
[36] Zhou L, Ma B and Han X. The role of autophagy in angiotensin II-induced pathological cardiac hypertrophy. J Mol Endocrinol 2016; 57: R143-R152.
[37] Kanzawa T, Germano IM, Komata T, Ito H, Kondo Y and Kondo S. Role of autophagy in temozolomide-induced cytotoxicity for malignant glioma cells. Cell Death Differ 2004; 11: 448-457.
[38] Nara A, Mizushima N, Yamamoto A, Kabeya Y, Ohsumi Y and Yoshimori T. SKD1 AAA ATPase-dependent endosomal transport is involved in autolysosome formation. Cell Struct Funct 2002; 27: 29-37.
[39] Choi J, Jo M, Lee E, Kim HJ and Choi D. Differential induction of autophagy by mTOR is associated with abnormal apoptosis in ovarian endometriotic cysts. Mol Hum Reprod 2014; 20: 309-317.
[40] Zhang L, Liu Y, Xu Y, Wu H, Wei Z and Cao Y. The expression of the autophagy gene beclin-1 mRNA and protein in ectopic and eutopic endometrium of patients with endometriosis. Int J Fertil Steril 2015; 8: 429-436.
[41] Burney RO and Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril 2012; 98: 511-519.
[42] Allavena G, Carrarelli P, Del Bello B, Luisi S, Petraglia F and Maellaro E. Autophagy is upregulated in ovarian endometriosis: a possible interplay with p53 and heme oxygenase-1. Fertil Steril 2015; 103: 1244-1251, e1241.
[43] Soares MP and Bach FH. Heme oxygenase-1: from biology to therapeutic potential. Trends Mol Med 2009; 15: 50-58.
[44] Vousden KH and Prives C. Blinded by the light: the growing complexity of p53. Cell 2009; 137: 413-431.
[45] Tasdemir E, Maiuri MC, Galluzzi L, Vitale I, Djavaheri-Mergny M, D'Amelio M, Criollo A, Morselli E, Zhu C, Harper F, Nannmark U, Samara C, Pinton P, Vicencio JM, Carnuccio R, Moll UM, Madeo F, Paterlini-Brechot P, Rizzuto R, Szabadkai G, Pierron G, Blomgren K, Tavernarakis N, Codogno P, Cecconi F and Kroemer G. Regulation of autophagy by cytoplasmic p53. Nat Cell Biol 2008; 10: 676-687.
[46] Morselli E, Shen S, Ruckenstuhl C, Bauer MA, Marino G, Galluzzi L, Criollo A, Michaud M, Maiuri MC, Chano T, Madeo F and Kroemer G. p53 inhibits autophagy by interacting with the human ortholog of yeast Atg17, RB1CC1/FIP200. Cell Cycle 2011; 10: 2763-2769.
[47] Liu H, Zhang Z, Xiong W, Zhang L, Xiong Y, Li N, He H, Du Y and Liu Y. HIF-1α promotes cells migration and invasion by upregulating autophagy in endometriosis. Reproduction 2017; 153: 809-820.
[48] Jung CH, Jun CB, Ro SH, Kim YM, Otto NM, Cao J, Kundu M and Kim DH. ULK-Atg13-FIP200

complexes mediate mTOR signaling to the autophagy machinery. Mol Biol Cell 2009; 20: 1992-2003.
[49] Kabeya Y, Mizushima N, Ueno T, Yamamoto A, Kirisako T, Noda T, Kominami E, Ohsumi Y and Yoshimori T. LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing. Embo J 2000; 19: 5720-5728.
[50] Burney RO, Talbi S, Hamilton AE, Vo KC, Nyegaard M, Nezhat CR, Lessey BA and Giudice LC. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. Endocrinology 2007; 148: 3814-3826.
[51] Feng Y, He D, Yao Z and Klionsky DJ. The machinery of macroautophagy. Cell Res 2014; 24: 24-41.
[52] Kang R, Zeh HJ, Lotze MT and Tang D. The Beclin 1 network regulates autophagy and apoptosis. Cell Death Differ 2011; 18: 571-580.
[53] Katagiri H, Nakayama K, Razia S, Nakamura K, Sato E, Ishibashi T, Ishikawa M, Iida K, Ishikawa N, Otsuki Y, Nakayama S and Kyo S. Loss of autophagy-related protein Beclin 1 may define poor prognosis in ovarian clear cell carcinomas. Int J Oncol 2015; 47: 2037-2044.
[54] Ren Y, Mu L, Ding X and Zheng W. Decreased expression of Beclin 1 in eutopic endometrium of women with adenomyosis. Arch Gynecol Obstet 2010; 282: 401-406.
[55] Kabeya Y, Mizushima N, Yamamoto A, Oshitani-Okamoto S, Ohsumi Y and Yoshimori T. LC3, GABARAP and GATE16 localize to autophagosomal membrane depending on form-II formation. J Cell Sci 2004; 117: 2805-2812.
[56] Levine B, Mizushima N and Virgin HW. Autophagy in immunity and inflammation. Nature 2011; 469: 323-335.
[57] Nasu K, Nishida M, Kawano Y, Tsuno A, Abe W, Yuge A, Takai N and Narahara H. Aberrant expression of apoptosis-related molecules in endometriosis: a possible mechanism underlying the pathogenesis of endometriosis. Reprod Sci 2011; 18: 206-218.
[58] Ghayad SE and Cohen PA. Inhibitors of the PI3K/Akt/mTOR pathway: new hope for breast cancer patients. Recent Pat Anticancer Drug Discov 2010; 5: 29-57.
[59] Honda H, Barrueto FF, Gogusev J, Im DD and Morin PJ. Serial analysis of gene expression reveals differential expression between endometriosis and normal endometrium. Possible roles for AXL and SHC1 in the pathogenesis of endometriosis. Reprod Biol Endocrinol 2008; 6: 59.
[60] Laudanski P, Szamatowicz J, Kowalczuk O, Kuzmicki M, Grabowicz M and Chyczewski L. Expression of selected tumor suppressor and oncogenes in endometrium of women with endometriosis. Hum Reprod 2009; 24: 1880-1890.
[61] Kim TH, Yu Y, Luo L, Lydon JP, Jeong JW and Kim JJ. Activated AKT pathway promotes establishment of endometriosis. Endocrinology 2014; 155: 1921-1930.
[62] Leconte M, Nicco C, Ngo C, Chereau C, Chouzenoux S, Marut W, Guibourdenche J, Arkwright S, Weill B, Chapron C, Dousset B and Batteux F. The mTOR/AKT inhibitor temsirolimus prevents deep infiltrating endometriosis in mice. Am J Pathol 2011; 179: 880-889.
[63] Chang CC, Hsieh YY, Tsai FJ, Tsai CH, Tsai HD and Lin CC. The proline form of p53 codon 72 polymorphism is associated with endometriosis. Fertil Steril 2002; 77: 43-45.
[64] Chipuk JE, Moldoveanu T, Llambi F, Parsons MJ and Green DR. The BCL-2 family reunion. Mol Cell 2010; 37: 299-310.
[65] Marino G, Niso-Santano M, Baehrecke EH and Kroemer G. Self-consumption: the interplay of autophagy and apoptosis. Nat Rev Mol Cell Biol 2014; 15: 81-94.
[66] Qu X, Zou Z, Sun Q, Luby-Phelps K, Cheng P, Hogan RN, Gilpin C and Levine B. Autophagy gene-dependent clearance of apoptotic cells during embryonic development. Cell 2007; 128: 931-946.
[67] Yu JJ, Sun HT, Zhang ZF, Shi RX, Liu LB, Shang WQ, Wei CY, Chang KK, Shao J, Wang MY and Li MQ. IL15 promotes growth and invasion of endometrial stromal cells and inhibits killing activity of NK cells in endometriosis. Reproduction 2016; 152: 151-160.
[68] Paludan C, Schmid D, Landthaler M, Vockerodt M, Kube D, Tuschl T and Munz C. Endogenous MHC class II processing of a viral nuclear antigen after autophagy. Science 2005; 307: 593-596.
[69] Ruiz A, Salvo VA, Ruiz LA, Baez P, Garcia M and Flores I. Basal and steroid hormone-regulated expression of CXCR4 in human endometrium and endometriosis. Reprod Sci 2010; 17: 894-903.
[70] Piao HL, Wang SC, Tao Y, Fu Q, Du MR and Li DJ. CXCL12/CXCR4 signal involved in the regulation of trophoblasts on peripheral NK cells leading to Th2 bias at the maternal-fetal interface. Eur Rev Med Pharmacol Sci 2015; 19: 2153-2161.
[71] Tao Y, Li YH, Piao HL, Zhou WJ, Zhang D, Fu Q, Wang SC, Li DJ and Du MR. CD56 (bright) CD25+ NK cells are preferentially recruited to the maternal/fetal interface in early human pregnancy. Cell Mol Immunol 2015; 12: 77-86.
[72] Wu X, Jin LP, Yuan MM, Zhu Y, Wang MY and Li DJ. Human first-trimester trophoblast cells recruit CD56brightCD16- NK cells into decidua

by way of expressing and secreting of CXCL12/stromal cell-derived factor 1. J Immunol 2005; 175: 61-68.
[73] Makker A, Goel MM, Das V and Agarwal A. PI3K-Akt-mTOR and MAPK signaling pathways in polycystic ovarian syndrome, uterine leiomyomas and endometriosis: an update. Gynecol Endocrinol 2012; 28: 175-181.
[74] Choi S, Shin H, Song H and Lim HJ. Suppression of autophagic activation in the mouse uterus by estrogen and progesterone. J Endocrinol 2014; 221: 39-50.
[75] Park J, Shin H, Song H and Lim HJ. Autophagic regulation in steroid hormone-responsive systems. Steroids 2016; 115: 177-181.
[76] Attia GR, Zeitoun K, Edwards D, Johns A, Carr BR and Bulun SE. Progesterone receptor isoform A but not B is expressed in endometriosis. J Clin Endocrinol Metab 2000; 85: 2897-2902.
[77] Bulun SE, Cheng YH, Yin P, Imir G, Utsunomiya H, Attar E, Innes J and Julie Kim J. Progesterone resistance in endometriosis: link to failure to metabolize estradiol. Mol Cell Endocrinol 2006; 248: 94-103.
[78] Rizner TL. Estrogen metabolism and action in endometriosis. Mol Cell Endocrinol 2009; 307: 8-18.
[79] Reis FM, Petraglia F and Taylor RN. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. Hum Reprod Update 2013; 19: 406-418.
[80] Cornillie FJ, Brosens IA, Vasquez G and Riphagen I. Histologic and ultrastructural changes in human endometriotic implants treated with the antiprogesterone steroid ethylnorgestrienone (gestrinone) during 2 months. Int J Gynecol Pathol 1986; 5: 95-109.
[81] Choi J, Jo M, Lee E, Lee DY and Choi D. Dienogest enhances autophagy induction in endometriotic cells by impairing activation of AKT, ERK1/2, and mTOR. Fertil Steril 2015; 104: 655-664, e651.
[82] Lipinski MM, Hoffman G, Ng A, Zhou W, Py BF, Hsu E, Liu X, Eisenberg J, Liu J, Blenis J, Xavier RJ and Yuan J. A genome-wide siRNA screen reveals multiple mTORC1 independent signaling pathways regulating autophagy under normal nutritional conditions. Dev Cell 2010; 18: 1041-1052.
[83] Okada S, Okada H, Sanezumi M, Nakajima T, Yasuda K and Kanzaki H. Expression of interleukin-15 in human endometrium and decidua. Mol Hum Reprod 2000; 6: 75-80.
[84] Lee SJ, Silverman E and Bargman JM. The role of antimalarial agents in the treatment of SLE and lupus nephritis. Nat Rev Nephrol 2011; 7: 718-729.
[85] Al-Bari MA. Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. J Antimicrob Chemother 2015; 70: 1608-1621.
[86] Amaravadi RK, Lippincott-Schwartz J, Yin XM, Weiss WA, Takebe N, Timmer W, DiPaola RS, Lotze MT and White E. Principles and current strategies for targeting autophagy for cancer treatment. Clin Cancer Res 2011; 17: 654-666.
[87] Calabretta B and Salomoni P. Inhibition of autophagy: a new strategy to enhance sensitivity of chronic myeloid leukemia stem cells to tyrosine kinase inhibitors. Leuk Lymphoma 2011; 52 Suppl 1: 54-59.
[88] Schmelzle T and Hall MN. TOR, a central controller of cell growth. Cell 2000; 103: 253-262.
[89] Chen N and Karantza V. Autophagy as a therapeutic target in cancer. Cancer Biol Ther 2011; 11: 157-168.
[90] Teixeira J, Maheswaran S and Donahoe PK. Mullerian inhibiting substance: an instructive developmental hormone with diagnostic and possible therapeutic applications. Endocr Rev 2001; 22: 657-674.
[91] Renaud EJ, MacLaughlin DT, Oliva E, Rueda BR and Donahoe PK. Endometrial cancer is a receptor-mediated target for mullerian inhibiting substance. Proc Natl Acad Sci U S A 2005; 102: 111-116.
[92] Borahay MA, Lu F, Ozpolat B, Tekedereli I, Gurates B, Karipcin S and Kilic GS. Mullerian inhibiting substance suppresses proliferation and induces apoptosis and autophagy in endometriosis cells in vitro. ISRN Obstet Gynecol 2013; 2013: 361489.
[93] Kim DK, Yang JS, Maiti K, Hwang JI, Kim K, Seen D, Ahn Y, Lee C, Kang BC, Kwon HB, Cheon J and Seong JY. A gonadotropin-releasing hormone-II antagonist induces autophagy of prostate cancer cells. Cancer Res 2009; 69: 923-931.
[94] Grundker C, Gunthert AR, Millar RP and Emons G. Expression of gonadotropin-releasing hormone II (GnRH-II) receptor in human endometrial and ovarian cancer cells and effects of GnRH-II on tumor cell proliferation. J Clin Endocrinol Metab 2002; 87: 1427-1430.
[95] Klionsky DJ, Abdalla FC, Abeliovich H, Abraham RT, Acevedo-Arozena A, Adeli K, Agholme L, Agnello M, Agostinis P, Aguirre-Ghiso JA, Ahn HJ, Ait-Mohamed O, Ait-Si-Ali S, Akematsu T, Akira S, Al-Younes HM, Al-Zeer MA, Albert ML, Albin RL, Alegre-Abarrategui J, Aleo MF, Alirezaei M, Almasan A, Almonte-Becerril M, Amano A, Amaravadi R, Amarnath S, Amer AO, Andrieu-Abadie N, Anantharam V, Ann DK, Anoopkumar-Dukie S, Aoki H, Apostolova N, Arancia G, Aris JP, Asanuma K, Asare NY, Ashida H, Askanas V, Askew DS, Auberger P, Baba M, Backues SK, Baehrecke EH, Bahr BA, Bai XY, Bailly Y, Baiocchi R, Baldini G, Balduini W, Ballabio A,

Bamber BA, Bampton ET, Banhegyi G, Bartholomew CR, Bassham DC, Bast RC Jr, Batoko H, Bay BH, Beau I, Bechet DM, Begley TJ, Behl C, Behrends C, Bekri S, Bellaire B, Bendall LJ, Benetti L, Berliocchi L, Bernardi H, Bernassola F, Besteiro S, Bhatia-Kissova I, Bi X, Biard-Piechaczyk M, Blum JS, Boise LH, Bonaldo P, Boone DL, Bornhauser BC, Bortoluci KR, Bossis I, Bost F, Bourquin JP, Boya P, Boyer-Guittaut M, Bozhkov PV, Brady NR, Brancolini C, Brech A, Brenman JE, Brennand A, Bresnick EH, Brest P, Bridges D, Bristol ML, Brookes PS, Brown EJ, Brumell JH, Brunetti-Pierri N, Brunk UT, Bulman DE, Bultman SJ, Bultynck G, Burbulla LF, Bursch W, Butchar JP, Buzgariu W, Bydlowski SP, Cadwell K, Cahova M, Cai D, Cai J, Cai Q, Calabretta B, Calvo-Garrido J, Camougrand N, Campanella M, Campos-Salinas J, Candi E, Cao L, Caplan AB, Carding SR, Cardoso SM, Carew JS, Carlin CR, Carmignac V, Carneiro LA, Carra S, Caruso RA, Casari G, Casas C, Castino R, Cebollero E, Cecconi F, Celli J, Chaachouay H, Chae HJ, Chai CY, Chan DC, Chan EY, Chang RC, Che CM, Chen CC, Chen GC, Chen GQ, Chen M, Chen Q, Chen SS, Chen W, Chen X, Chen X, Chen X, Chen YG, Chen Y, Chen Y, Chen YJ, Chen Z, Cheng A, Cheng CH, Cheng Y, Cheong H, Cheong JH, Cherry S, Chess-Williams R, Cheung ZH, Chevet E, Chiang HL, Chiarelli R, Chiba T, Chin LS, Chiou SH, Chisari FV, Cho CH, Cho DH, Choi AM, Choi D, Choi KS, Choi ME, Chouaib S, Choubey D, Choubey V, Chu CT, Chuang TH, Chueh SH, Chun T, Chwae YJ, Chye ML, Ciarcia R, Ciriolo MR, Clague MJ, Clark RS, Clarke PG, Clarke R, Codogno P, Coller HA, Colombo MI, Comincini S, Condello M, Condorelli F, Cookson MR, Coombs GH, Coppens I, Corbalan R, Cossart P, Costelli P, Costes S, Coto-Montes A, Couve E, Coxon FP, Cregg JM, Crespo JL, Cronje MJ, Cuervo AM, Cullen JJ, Czaja MJ, D'Amelio M, Darfeuille-Michaud A, Davids LM, Davies FE, De Felici M, de Groot JF, de Haan CA, De Martino L, De Milito A, De Tata V, Debnath J, Degterev A, Dehay B, Delbridge LM, Demarchi F, Deng YZ, Dengjel J, Dent P, Denton D, Deretic V, Desai SD, Devenish RJ, Di Gioacchino M, Di Paolo G, Di Pietro C, Diaz-Araya G, Diaz-Laviada I, Diaz-Meco MT, Diaz-Nido J, Dikic I, Dinesh-Kumar SP, Ding WX, Distelhorst CW, Diwan A, Djavaheri-Mergny M, Dokudovskaya S, Dong Z, Dorsey FC, Dosenko V, Dowling JJ, Doxsey S, Dreux M, Drew ME, Duan Q, Duchosal MA, Duff K, Dugail I, Durbeej M, Duszenko M, Edelstein CL, Edinger AL, Egea G, Eichinger L, Eissa NT, Ekmekcioglu S, El-Deiry WS, Elazar Z, Elgendy M, Ellerby LM, Eng KE, Engelbrecht AM, Engelender S, Erenpreisa J, Escalante R, Esclatine A, Eskelinen EL, Espert L, Espina V, Fan H, Fan J, Fan QW, Fan Z, Fang S, Fang Y, Fanto M, Fanzani A, Farkas T, Farre JC, Faure M, Fechheimer M, Feng CG, Feng J, Feng Q, Feng Y, Fesus L, Feuer R, Figueiredo-Pereira ME, Fimia GM, Fingar DC, Finkbeiner S, Finkel T, Finley KD, Fiorito F, Fisher EA, Fisher PB, Flajolet M, Florez-McClure ML, Florio S, Fon EA, Fornai F, Fortunato F, Fotedar R, Fowler DH, Fox HS, Franco R, Frankel LB, Fransen M, Fuentes JM, Fueyo J, Fujii J, Fujisaki K, Fujita E, Fukuda M, Furukawa RH, Gaestel M, Gailly P, Gajewska M, Galliot B, Galy V, Ganesh S, Ganetzky B, Ganley IG, Gao FB, Gao GF, Gao J, Garcia L, Garcia-Manero G, Garcia-Marcos M, Garmyn M, Gartel AL, Gatti E, Gautel M, Gawriluk TR, Gegg ME, Geng J, Germain M, Gestwicki JE, Gewirtz DA, Ghavami S, Ghosh P, Giammarioli AM, Giatromanolaki AN, Gibson SB, Gilkerson RW, Ginger ML, Ginsberg HN, Golab J, Goligorsky MS, Golstein P, Gomez-Manzano C, Goncu E, Gongora C, Gonzalez CD, Gonzalez R, Gonzalez-Estevez C, Gonzalez-Polo RA, Gonzalez-Rey E, Gorbunov NV, Gorski S, Goruppi S, Gottlieb RA, Gozuacik D, Granato GE, Grant GD, Green KN, Gregorc A, Gros F, Grose C, Grunt TW, Gual P, Guan JL, Guan KL, Guichard SM, Gukovskaya AS, Gukovsky I, Gunst J, Gustafsson AB, Halayko AJ, Hale AN, Halonen SK, Hamasaki M, Han F, Han T, Hancock MK, Hansen M, Harada H, Harada M, Hardt SE, Harper JW, Harris AL, Harris J, Harris SD, Hashimoto M, Haspel JA, Hayashi S, Hazelhurst LA, He C, He YW, Hebert MJ, Heidenreich KA, Helfrich MH, Helgason GV, Henske EP, Herman B, Herman PK, Hetz C, Hilfiker S, Hill JA, Hocking LJ, Hofman P, Hofmann TG, Hohfeld J, Holyoake TL, Hong MH, Hood DA, Hotamisligil GS, Houwerzijl EJ, Hoyer-Hansen M, Hu B, Hu CA, Hu HM, Hua Y, Huang C, Huang J, Huang S, Huang WP, Huber TB, Huh WK, Hung TH, Hupp TR, Hur GM, Hurley JB, Hussain SN, Hussey PJ, Hwang JJ, Hwang S, Ichihara A, Ilkhanizadeh S, Inoki K, Into T, Iovane V, Iovanna JL, Ip NY, Isaka Y, Ishida H, Isidoro C, Isobe K, Iwasaki A, Izquierdo M, Izumi Y, Jaakkola PM, Jaattela M, Jackson GR, Jackson WT, Janji B, Jendrach M, Jeon JH, Jeung EB, Jiang H, Jiang H, Jiang JX, Jiang M, Jiang Q, Jiang X, Jiang X, Jimenez A, Jin M, Jin S, Joe CO, Johansen T, Johnson DE, Johnson GV, Jones NL, Joseph B, Joseph SK, Joubert AM, Juhasz G, Juillerat-Jeanneret L, Jung CH, Jung YK, Kaarniranta K, Kaasik A, Kabuta T, Kadowaki M, Kagedal K, Kamada Y, Kaminskyy VO, Kampinga HH, Kanamori H, Kang C, Kang KB, Kang KI, Kang R, Kang YA, Kanki T, Kanneganti TD, Kanno H, Kanthasamy AG, Kanthasamy A, Karantza V, Kaushal GP, Kaushik S, Kawazoe Y, Ke PY, Kehrl JH, Kelekar A, Kerkhoff C, Kessel DH, Khalil H, Kiel JA,

Kiger AA, Kihara A, Kim DR, Kim DH, Kim DH, Kim EK, Kim HR, Kim JS, Kim JH, Kim JC, Kim JK, Kim PK, Kim SW, Kim YS, Kim Y, Kimchi A, Kimmelman AC, King JS, Kinsella TJ, Kirkin V, Kirshenbaum LA, Kitamoto K, Kitazato K, Klein L, Klimecki WT, Klucken J, Knecht E, Ko BC, Koch JC, Koga H, Koh JY, Koh YH, Koike M, Komatsu M, Kominami E, Kong HJ, Kong WJ, Korolchuk VI, Kotake Y, Koukourakis MI, Kouri Flores JB, Kovacs AL, Kraft C, Krainc D, Kramer H, Kretz-Remy C, Krichevsky AM, Kroemer G, Kruger R, Krut O, Ktistakis NT, Kuan CY, Kucharczyk R, Kumar A, Kumar R, Kumar S, Kundu M, Kung HJ, Kurz T, Kwon HJ, La Spada AR, Lafont F, Lamark T, Landry J, Lane JD, Lapaquette P, Laporte JF, Laszlo L, Lavandero S, Lavoie JN, Layfield R, Lazo PA, Le W, Le Cam L, Ledbetter DJ, Lee AJ, Lee BW, Lee GM, Lee J, Lee JH, Lee M, Lee MS, Lee SH, Leeuwenburgh C, Legembre P, Legouis R, Lehmann M, Lei HY, Lei QY, Leib DA, Leiro J, Lemasters JJ, Lemoine A, Lesniak MS, Lev D, Levenson VV, Levine B, Levy E, Li F, Li JL, Li L, Li S, Li W, Li XJ, Li YB, Li YP, Liang C, Liang Q, Liao YF, Liberski PP, Lieberman A, Lim HJ, Lim KL, Lim K, Lin CF, Lin FC, Lin J, Lin JD, Lin K, Lin WW, Lin WC, Lin YL, Linden R, Lingor P, Lippincott-Schwartz J, Lisanti MP, Liton PB, Liu B, Liu CF, Liu K, Liu L, Liu QA, Liu W, Liu YC, Liu Y, Lockshin RA, Lok CN, Lonial S, Loos B, Lopez-Berestein G, Lopez-Otin C, Lossi L, Lotze MT, Low P, Lu B, Lu B, Lu B, Lu Z, Luciano F, Lukacs NW, Lund AH, Lynch-Day MA, Ma Y, Macian F, MacKeigan JP, Macleod KF, Madeo F, Maiuri L, Maiuri MC, Malagoli D, Malicdan MC, Malorni W, Man N, Mandelkow EM, Manon S, Manov I, Mao K, Mao X, Mao Z, Marambaud P, Marazziti D, Marcel YL, Marchbank K, Marchetti P, Marciniak SJ, Marcondes M, Mardi M, Marfe G, Marino G, Markaki M, Marten MR, Martin SJ, Martinand-Mari C, Martinet W, Martinez-Vicente M, Masini M, Matarrese P, Matsuo S, Matteoni R, Mayer A, Mazure NM, McConkey DJ, McConnell MJ, McDermott C, McDonald C, McInerney GM, McKenna SL, McLaughlin B, McLean PJ, McMaster CR, McQuibban GA, Meijer AJ, Meisler MH, Melendez A, Melia TJ, Melino G, Mena MA, Menendez JA, Menna-Barreto RF, Menon MB, Menzies FM, Mercer CA, Merighi A, Merry DE, Meschini S, Meyer CG, Meyer TF, Miao CY, Miao JY, Michels PA, Michiels C, Mijaljica D, Milojkovic A, Minucci S, Miracco C, Miranti CK, Mitroulis I, Miyazawa K, Mizushima N, Mograbi B, Mohseni S, Molero X, Mollereau B, Mollinedo F, Momoi T, Monastyrska I, Monick MM, Monteiro MJ, Moore MN, Mora R, Moreau K, Moreira PI, Moriyasu Y, Moscat J, Mostowy S, Mottram JC, Motyl T, Moussa CE, Muller S, Muller S, Munger K, Munz C, Murphy LO, Murphy ME, Musaro A, Mysorekar I, Nagata E, Nagata K, Nahimana A, Nair U, Nakagawa T, Nakahira K, Nakano H, Nakatogawa H, Nanjundan M, Naqvi NI, Narendra DP, Narita M, Navarro M, Nawrocki ST, Nazarko TY, Nemchenko A, Netea MG, Neufeld TP, Ney PA, Nezis IP, Nguyen HP, Nie D, Nishino I, Nislow C, Nixon RA, Noda T, Noegel AA, Nogalska A, Noguchi S, Notterpek L, Novak I, Nozaki T, Nukina N, Nurnberger T, Nyfeler B, Obara K, Oberley TD, Oddo S, Ogawa M, Ohashi T, Okamoto K, Oleinick NL, Oliver FJ, Olsen LJ, Olsson S, Opota O, Osborne TF, Ostrander GK, Otsu K, Ou JH, Ouimet M, Overholtzer M, Ozpolat B, Paganetti P, Pagnini U, Pallet N, Palmer GE, Palumbo C, Pan T, Panaretakis T, Pandey UB, Papackova Z, Papassideri I, Paris I, Park J, Park OK, Parys JB, Parzych KR, Patschan S, Patterson C, Pattingre S, Pawelek JM, Peng J, Perlmutter DH, Perrotta I, Perry G, Pervaiz S, Peter M, Peters GJ, Petersen M, Petrovski G, Phang JM, Piacentini M, Pierre P, Pierrefite-Carle V, Pierron G, Pinkas-Kramarski R, Piras A, Piri N, Platanias LC, Poggeler S, Poirot M, Poletti A, Pous C, Pozuelo-Rubio M, Praetorius-Ibba M, Prasad A, Prescott M, Priault M, Produit-Zengaffinen N, Progulske-Fox A, Proikas-Cezanne T, Przedborski S, Przyklenk K, Puertollano R, Puyal J, Qian SB, Qin L, Qin ZH, Quaggin SE, Raben N, Rabinowich H, Rabkin SW, Rahman I, Rami A, Ramm G, Randall G, Randow F, Rao VA, Rathmell JC, Ravikumar B, Ray SK, Reed BH, Reed JC, Reggiori F, Regnier-Vigouroux A, Reichert AS, Reiners JJ Jr, Reiter RJ, Ren J, Revuelta JL, Rhodes CJ, Ritis K, Rizzo E, Robbins J, Roberge M, Roca H, Roccheri MC, Rocchi S, Rodemann HP, Rodriguez de Cordoba S, Rohrer B, Roninson IB, Rosen K, Rost-Roszkowska MM, Rouis M, Rouschop KM, Rovetta F, Rubin BP, Rubinsztein DC, Ruckdeschel K, Rucker EB, 3rd, Rudich A, Rudolf E, Ruiz-Opazo N, Russo R, Rusten TE, Ryan KM, Ryter SW, Sabatini DM, Sadoshima J, Saha T, Saitoh T, Sakagami H, Sakai Y, Salekdeh GH, Salomoni P, Salvaterra PM, Salvesen G, Salvioli R, Sanchez AM, Sanchez-Alcazar JA, Sanchez-Prieto R, Sandri M, Sankar U, Sansanwal P, Santambrogio L, Saran S, Sarkar S, Sarwal M, Sasakawa C, Sasnauskiene A, Sass M, Sato K, Sato M, Schapira AH, Scharl M, Schatzl HM, Scheper W, Schiaffino S, Schneider C, Schneider ME, Schneider-Stock R, Schoenlein PV, Schorderet DF, Schuller C, Schwartz GK, Scorrano L, Sealy L, Seglen PO, Segura-Aguilar J, Seiliez I, Seleverstov O, Sell C, Seo JB, Separovic D, Setaluri V, Setoguchi T, Settembre C, Shacka JJ, Shanmugam M, Shapiro IM, Shaulian E, Shaw RJ, Shelhamer JH, Shen HM, Shen WC,

Sheng ZH, Shi Y, Shibuya K, Shidoji Y, Shieh JJ, Shih CM, Shimada Y, Shimizu S, Shintani T, Shirihai OS, Shore GC, Sibirny AA, Sidhu SB, Sikorska B, Silva-Zacarin EC, Simmons A, Simon AK, Simon HU, Simone C, Simonsen A, Sinclair DA, Singh R, Sinha D, Sinicrope FA, Sirko A, Siu PM, Sivridis E, Skop V, Skulachev VP, Slack RS, Smaili SS, Smith DR, Soengas MS, Soldati T, Song X, Sood AK, Soong TW, Sotgia F, Spector SA, Spies CD, Springer W, Srinivasula SM, Stefanis L, Steffan JS, Stendel R, Stenmark H, Stephanou A, Stern ST, Sternberg C, Stork B, Stralfors P, Subauste CS, Sui X, Sulzer D, Sun J, Sun SY, Sun ZJ, Sung JJ, Suzuki K, Suzuki T, Swanson MS, Swanton C, Sweeney ST, Sy LK, Szabadkai G, Tabas I, Taegtmeyer H, Tafani M, Takacs-Vellai K, Takano Y, Takegawa K, Takemura G, Takeshita F, Talbot NJ, Tan KS, Tanaka K, Tanaka K, Tang D, Tang D, Tanida I, Tannous BA, Tavernarakis N, Taylor GS, Taylor GA, Taylor JP, Terada LS, Terman A, Tettamanti G, Thevissen K, Thompson CB, Thorburn A, Thumm M, Tian F, Tian Y, Tocchini-Valentini G, Tolkovsky AM, Tomino Y, Tonges L, Tooze SA, Tournier C, Tower J, Towns R, Trajkovic V, Travassos LH, Tsai TF, Tschan MP, Tsubata T, Tsung A, Turk B, Turner LS, Tyagi SC, Uchiyama Y, Ueno T, Umekawa M, Umemiya-Shirafuji R, Unni VK, Vaccaro MI, Valente EM, Van den Berghe G, van der Klei IJ, van Doorn W, van Dyk LF, van Egmond M, van Grunsven LA, Vandenabeele P, Vandenberghe WP, Vanhorebeek I, Vaquero EC, Velasco G, Vellai T, Vicencio JM, Vierstra RD, Vila M, Vindis C, Viola G, Viscomi MT, Voitsekhovskaja OV, von Haefen C, Votruba M, Wada K, Wade-Martins R, Walker CL, Walsh CM, Walter J, Wan XB, Wang A, Wang C, Wang D, Wang F, Wang F, Wang G, Wang H, Wang HG, Wang HD, Wang J, Wang K, Wang M, Wang RC, Wang X, Wang X, Wang YJ, Wang Y, Wang Z, Wang ZC, Wang Z, Wansink DG, Ward DM, Watada H, Waters SL, Webster P, Wei L, Weihl CC, Weiss WA, Welford SM, Wen LP, Whitehouse CA, Whitton JL, Whitworth AJ, Wileman T, Wiley JW, Wilkinson S, Willbold D, Williams RL, Williamson PR, Wouters BG, Wu C, Wu DC, Wu WK, Wyttenbach A, Xavier RJ, Xi Z, Xia P, Xiao G, Xie Z, Xie Z, Xu DZ, Xu J, Xu L, Xu X, Yamamoto A, Yamamoto A, Yamashina S, Yamashita M, Yan X, Yanagida M, Yang DS, Yang E, Yang JM, Yang SY, Yang W, Yang WY, Yang Z, Yao MC, Yao TP, Yeganeh B, Yen WL, Yin JJ, Yin XM, Yoo OJ, Yoon G, Yoon SY, Yorimitsu T, Yoshikawa Y, Yoshimori T, Yoshimoto K, You HJ, Youle RJ, Younes A, Yu L, Yu L, Yu SW, Yu WH, Yuan ZM, Yue Z, Yun CH, Yuzaki M, Zabirnyk O, Silva-Zacarin E, Zacks D, Zacksenhaus E, Zaffaroni N, Zakeri Z, Zeh HJ 3rd, Zeitlin SO, Zhang H, Zhang HL, Zhang J, Zhang JP, Zhang L, Zhang L, Zhang MY, Zhang XD, Zhao M, Zhao YF, Zhao Y, Zhao ZJ, Zheng X, Zhivotovsky B, Zhong Q, Zhou CZ, Zhu C, Zhu WG, Zhu XF, Zhu X, Zhu Y, Zoladek T, Zong WX, Zorzano A, Zschocke J and Zuckerbraun B. Guidelines for the use and interpretation of assays for monitoring autophagy. Autophagy 2012; 8: 445-544.

[96] Mauvezin C, Nagy P, Juhasz G and Neufeld TP. Autophagosome-lysosome fusion is independent of V-ATPase-mediated acidification. Nat Commun 2015; 6: 7007.

[97] Yamamoto A, Tagawa Y, Yoshimori T, Moriyama Y, Masaki R and Tashiro Y. Bafilomycin A1 prevents maturation of autophagic vacuoles by inhibiting fusion between autophagosomes and lysosomes in rat hepatoma cell line, H-4-II-E cells. Cell Struct Funct 1998; 23: 33-42.

[98] Martinez-Outschoorn UE, Trimmer C, Lin Z, Whitaker-Menezes D, Chiavarina B, Zhou J, Wang C, Pavlides S, Martinez-Cantarin MP, Capozza F, Witkiewicz AK, Flomenberg N, Howell A, Pestell RG, Caro J, Lisanti MP and Sotgia F. Autophagy in cancer associated fibroblasts promotes tumor cell survival: Role of hypoxia, HIF1 induction and NFkappaB activation in the tumor stromal microenvironment. Cell Cycle 2010; 9: 3515-3533.

[99] Hsiao KY, Lin SC, Wu MH and Tsai SJ. Pathological functions of hypoxia in endometriosis. Front Biosci (Elite Ed) 2015; 7: 309-321.

[100] Lu Z, Zhang W, Jiang S, Zou J and Li Y. Effect of oxygen tensions on the proliferation and angiogenesis of endometriosis heterograft in severe combined immunodeficiency mice. Fertil Steril 2014; 101: 568-576.

[101] Turgut A, Ozler A, Goruk NY, Tunc SY, Evliyaoglu O and Gul T. Copper, ceruloplasmin and oxidative stress in patients with advanced-stage endometriosis. Eur Rev Med Pharmacol Sci 2013; 17: 1472-1478.

[102] Dai L, Lou W, Zhu J, Zhou X and Di W. MiR-199a inhibits the angiogenic potential of endometrial stromal cells under hypoxia by targeting HIF-1alpha/VEGF pathway. Int J Clin Exp Pathol 2015; 8: 4735-4744.

[103] Lin SC, Wang CC, Wu MH, Yang SH, Li YH and Tsai SJ. Hypoxia-induced microRNA-20a expression increases ERK phosphorylation and angiogenic gene expression in endometriotic stromal cells. J Clin Endocrinol Metab 2012; 97: E1515-1523.

[104] Xu TX, Zhao SZ, Dong M and Yu XR. Hypoxia responsive miR-210 promotes cell survival and autophagy of endometriotic cells in hypoxia. Eur Rev Med Pharmacol Sci 2016; 20: 399-406.

[105] Tenhunen R, Marver HS and Schmid R. The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase. Proc Natl Acad Sci U S A 1968; 61: 748-755.
[106] Corcelle EA, Puustinen P and Jaattela M. Apoptosis and autophagy: targeting autophagy signalling in cancer cells -'trick or treats'? Febs J 2009; 276: 6084-6096.
[107] Banu SK, Lee J, Speights VO Jr, Starzinski-Powitz A and Arosh JA. Selective inhibition of prostaglandin E2 receptors EP2 and EP4 induces apoptosis of human endometriotic cells through suppression of ERK1/2, AKT, NFkappaB, and beta-catenin pathways and activation of intrinsic apoptotic mechanisms. Mol Endocrinol 2009; 23: 1291-1305.
[108] Yin X, Pavone ME, Lu Z, Wei J and Kim JJ. Increased activation of the PI3K/AKT pathway compromises decidualization of stromal cells from endometriosis. J Clin Endocrinol Metab 2012; 97: E35-43.
[109] Zhang H, Zhao X, Liu S, Li J, Wen Z and Li M. 17betaE2 promotes cell proliferation in endometriosis by decreasing PTEN via NFkappaB-dependent pathway. Mol Cell Endocrinol 2010; 317: 31-43.
[110] Yagyu T, Tsuji Y, Haruta S, Kitanaka T, Yamada Y, Kawaguchi R, Kanayama S, Tanase Y, Kurita N and Kobayashi H. Activation of mammalian target of rapamycin in postmenopausal ovarian endometriosis. Int J Gynecol Cancer 2006; 16: 1545-1551.