Oxidative stress as a nexus: Integrating mitophagy and ferroptosis in endometrial carcinogenesis (Review)

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Abstract. Endometrial cancer (EC), a malignancy of the uterine lining with rising global incidence that is linked to obesity and metabolic syndrome, is molecularly stratified into four The Cancer Genome Atlas subtypes (DNA polymerase ε ultramutated, microsatellite instability-high, copy-number low and copy-number high), each requiring tailored therapeutic strategies. Despite advancements, drug resistance remains a critical challenge, prompting exploration of regulated cell death pathways such as ferroptosis, an iron-driven process marked by lipid peroxidation and glutathione peroxidase 4 (GPX4) inactivation. Mitochondrial dysfunction, a hallmark of EC, exacerbates oxidative stress by disrupting fission/fusion dynamics (via dynamin-related protein 1/mitofusin 1/2 imbalance) and impairing mitophagy (through PTEN-induced kinase 1/Parkin or FUN14 domain-containing protein 1 pathway defects), thereby promoting iron overload and ferroptotic vulnerability. Reactive oxygen species (ROS), generated via mitochondrial electron transport chains and NADPH oxidases, exhibit dual roles: Moderate levels drive tumorigenesis through DNA damage and immune evasion, while excessive ROS levels induce ferroptosis by depleting antioxidants (such as glutathione) and amplifying lipid peroxidation. The present review systematically integrates evidence on mitophagy and ferroptosis in EC pathogenesis; it highlights oxidative stress as a central nexus linking mitochondrial surveillance failure (such as cristae collapse and BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like-mediated mitophagy in TP53-mutant tumors) to iron-dependent membrane damage (via acyl-CoA synthetase long-chain family member 4 and ferroptosis suppressor protein 1-coenzyme Q10 dysregulation). Emerging therapeutic strategies targeting redox-sensitive nodes, including GPX4 degraders, mitophagy inducers (urolithin A) and chronotherapy, have the potential to overcome resistance. By elucidating the crosstalk between mitochondrial quality control and ferroptotic signaling, the present review provides a mechanistic framework for precision oncology in EC, emphasizing subtype-specific vulnerabilities and spatiotemporal redox profiling.

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Abbreviations: ACSL4, acyl-CoA synthetase long-chain family member 4; AMPK, AMP-activated protein kinase; BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; BNIP3L/NIX, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like; CoQ10, Coenzyme Q10; CSCs, cancer stem cells; EC, endometrial cancer; EMT, epithelial-mesenchymal transition; ERα, estrogen receptor α; Fe-S, iron-sulfur cluster; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; FUNDC1, FUN14 domain-containing protein 1; GPX4, GSH peroxidase 4; GPx, GSH peroxidase; GSH, glutathione; HIF, hypoxia-inducible factor; ISCU, iron-sulfur cluster assembly enzyme; Keap1, Kelch-like ECH-associated protein 1; LC3, microtubule-associated proteins 1A/1B light chain 3B; MSI-H, microsatellite instability-high; mtDNA, mitochondrial DNA; Nrf2, nuclear factor erythroid 2-related factor 2; OMM, outer mitochondrial membrane; p62/SQSTM1, Sequestosome 1; PDX, patient-derived xenograft; PINK1, PTEN-induced kinase 1; POLE, DNA polymerase ε; RCD, regulated cell death; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; TCGA, The Cancer Genome Atlas; TFR1, transferrin receptor 1; Ub, ubiquitin; ULK1, Unc-51 like autophagy activating kinase 1

Key words: ferroptosis, mitochondrial dynamics, mitophagy, oxidative stress, endometrial cancer, TCGA molecular subtypes, lipid peroxidation, ROS, precision therapy, drug resistance

Contents

1. Introduction

Endometrial cancer (EC), a malignancy originating from the uterine endometrium, exhibits a rising global incidence,

with >417,000 new cases and 97,000 deaths reported worldwide in 2022 alone (1). This trend is largely attributable to the increasing prevalence of risk factors such as obesity and metabolic syndrome (1-3). Therapeutically, EC management has been refined by the molecular classification established by The Cancer Genome Atlas (TCGA), which categorizes EC into four subtypes [DNA polymerase ε (POLE) ultramutated, microsatellite instability-high (MSI-H), copy-number low and copy-number high], each with distinct prognoses and therapeutic implications (4-6). This classification provides a critical basis for personalized therapy (7,8). Surgical intervention remains the cornerstone of EC management. Chemotherapy is mainly reserved for cases with advanced or recurrent disease, as well as for patients with high-risk pathological features post-surgery. Nevertheless, chemoresistance development presents a major therapeutic challenge (9), leading to treatment failure and mortality in >90% of patients with advanced-stage disease. A notable clinical limitation is the lack of effective prognostic biomarkers and specific targets to overcome chemoresistance (10). Dysregulation of regulated cell death (RCD) mechanisms is a recognized cancer hallmark, contributing to tumor progression and drug resistance. Emerging evidence has indicated novel RCD pathways, including autophagy, ferroptosis and pyroptosis, as potential therapeutic targets to enhance therapeutic efficacy and reverse chemoresistance in EC (11-16).

Reactive oxygen species (ROS), primarily generated via mitochondrial electron transport chain activity (17,18), NADPH oxidases (19) and exogenous stressors, exhibit a dual role in cancer initiation, progression, suppression and therapy (20). Oxidative stress, defined as an imbalance between ROS production and elimination, is a critical pathogenic factor in numerous chronic diseases, including cancer (21), cardiovascular diseases (22,23), metabolic disorders (24) and neurodegenerative conditions (such as Alzheimer's and Parkinson's diseases) (25). Depending on their levels and cellular context, ROS can promote tumorigenesis by inducing DNA damage, epithelial-mesenchymal transition (EMT) and immune evasion, or suppress tumor growth by triggering cell death pathways such as apoptosis and ferroptosis (20,26).

Ferroptosis is an iron-dependent form of RCD marked by iron accumulation and extensive lipid peroxidation. Key morphological characteristics include condensed cellular membranes, with increased density and reduction, or loss of mitochondrial cristae (27). Ferroptosis involves disruption of redox homeostasis, marked by depleted antioxidants [such as glutathione (GSH) and GSH peroxidase 4 (GPX4)] and accumulation of oxidants (such as Fe^{2+} and lipid ROS) (28). As primary intracellular ROS sources, mitochondria are intrinsically linked to ferroptosis. Mitophagy, a selective autophagic process that degrades damaged mitochondria via ubiquitin (Ub)-dependent or -independent pathways, serves as a protective mechanism against stress and is crucial for mitochondrial quality control (29-32). Mitophagy and ferroptosis, as two distinct forms of RCD, have been increasingly implicated in EC (11,16,33,34). Concurrently, oxidative stress, a key regulator of cellular metabolism, is closely linked to EC progression (35,36). The triad of mitophagy, ferroptosis and oxidative stress forms a dynamic equilibrium, collectively contributing to the pathogenesis of diverse diseases through their interconnected regulatory networks (37,38). The present review aims to delineate the role of oxidative stress as a central hub integrating mitophagy and ferroptosis in EC pathogenesis, offering novel perspectives for its prevention and treatment.

2. Molecular mechanisms of oxidative stress and their role in cancer

ROS generation and scavenging systems. ROS, including superoxide anions, free radicals and hydrogen peroxide, are highly reactive molecules generated primarily through mitochondrial electron transport and NADPH oxidase activity (16-19,38,39). Additional sources include peroxisomal metabolism and endoplasmic reticulum stress (40,41). Oxidative stress occurs due to a disruption in the balance between ROS generation and clearance, serving a notable role in the development of cancer (21-23). Cellular protection against ROS involves a multi-level defense system, including enzymatic antioxidants (such as superoxide dismutase, catalase and GSH peroxidase), non-enzymatic scavengers (such as vitamin C, vitamins E and GSH) and repair systems for oxidized biomolecules, which collectively maintain redox homeostasis (39).

Pro-tumorigenic and tumor-suppressive functions of oxidative stress. Physiological ROS levels regulate essential cellular processes (including proliferation, differentiation, survival and apoptosis). However, supraphysiological ROS levels drive tumorigenesis and progression (42,43). Excessive endogenous or exogenous ROS levels induce direct DNA damage and impair DNA repair mechanisms, causing mutations that inactivate tumor suppressors (such as p53) or activate oncogenes (such as KRAS) (44-46).

ROS further promote malignancy by activating proliferative signaling (including the PI3K/AKT/mTOR and MAPK pathways), and suppressing antitumor immunity via impaired T-cell differentiation/activation, T-cell death, natural killer cell dysfunction and M2 macrophage polarization/recruitment (47,48). ROS facilitate invasion and metastasis through EMT, and induce EMT-associated cytoskeletal rearrangement (Rho GTPase-dependent), extracellular matrix degradation (matrix metalloproteinase-dependent) and angiogenesis [hypoxia-inducible factor (HIF)-dependent] (49).

Although high ROS levels are crucial in promoting tumor initiation and progression, excessive ROS levels also serve an antioncogenic role in cancer (26,50). Excessively accumulated ROS repress cancer cell growth by inhibiting cancer cell proliferation through disrupting nucleotide/ATP synthesis and inducing cell cycle arrest (51). ROS also trigger tumor cell death by activating endoplasmic reticulum stress-mediated, mitochondrial and p53-dependent apoptotic pathways, along with the ferroptosis pathway (26). Therefore, targeting the regulation of ROS levels (for example, using pro-oxidant agents or inhibiting antioxidant pathways) has emerged as a novel therapeutic strategy in cancer treatment, aiming to exploit the 'dual role' of oxidative stress to achieve selective elimination of tumor cells.

3. Dual role of mitophagy in EC

Core mechanisms of mitophagy. Mitophagy represents a selective type of autophagy that functions as a protective

response to intracellular and extracellular stress signals (32). Mitophagy maintains mitochondrial and cellular homeostasis by eliminating dysfunctional mitochondria, including depolarized, damaged or superfluous organelles, through lysosomal degradation. The core molecular mechanisms can be divided into Ub-dependent pathways and Ub-independent pathways (31). The PTEN-induced kinase 1 (PINK1)/Parkin pathway represents the most well-characterized Ub-dependent mechanism. Upon mitochondrial depolarization or damage, PINK1 stabilizes on the outer mitochondrial membrane (OMM), and phosphorylates Ub and the E3 Ub ligase Parkin, leading to the ubiquitination of OMM proteins. Autophagy receptors such as p62/sequestosome 1 (SQSTM1) and optineurin then recognize ubiquitinated substrates and link them to microtubule-associated proteins 1A/1B light chain 3B (LC3)-positive autophagosomal membranes for engulfment (31). Alternatively, Ub-independent pathways utilize OMM-resident receptors, including BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), BNIP3L (also known as NIX) and FUN14 domain-containing protein 1 (FUNDC1), which directly interact with LC3/GABA type A receptor-associated protein via LC3-interacting regions to initiate mitophagy. These coordinated mechanisms ensure the precise elimination of dysfunctional mitochondria, and their dysregulation is broadly implicated in various pathological states, including cancer (30,52,53).

Pro-tumorigenic and tumor-suppressive functions of mitophagy. Mitophagy is widely reported to exhibit aberrant activity levels in various cancer types compared with under normal physiological conditions (54,55). Current research has revealed its dual role in cancer biology, demonstrating both tumor-promoting and tumor-suppressive functions depending on the cellular context (56,57). In its pro-tumorigenic capacity, mitophagy is known to enable cancer cell survival under stress and facilitates malignant progression by clearing dysfunctional mitochondria (58). Under hypoxia, mitophagy mediated by BNIP3 and NIX is known to enhance tumor aggressiveness by lowering mitochondrial ROS levels, stabilizing HIF-1α, promoting glycolytic shift and inducing EMT, which collectively increase invasiveness and metastatic potential (59). Chemotherapy- or radiotherapy-induced mitochondrial damage can activate the PINK1/Parkin pathway, which ubiquitinates damaged mitochondria to block cytochrome c release, thereby potentially enabling cancer cells to evade apoptosis and develop therapeutic resistance (60). During metastasis, FUNDC1-dependent mitophagy is suggested to optimize energy metabolism to fuel ATP production, supporting cancer cell migration and invasion (61). Additionally, mitophagy may suppress NLR family pyrin domain containing 3 (NLRP3) inflammasome activation by removing mitochondrial damage-associated molecular patterns [mitochondrial DNA (mtDNA) and cardiolipin], thereby reducing secretion of the pro-inflammatory cytokine IL-1β and impairing antitumor immunity to promote immune evasion (62).

Conversely, mitophagy also exerts tumor-suppressive effects, as supported by multiple lines of evidence (59,63). In precancerous or early-stage tumors, mitophagy impedes malignant transformation by eliminating mitochondria harboring oncogenic damage. For example, mtDNA mutations, which drive early carcinogenesis, are selectively cleared via NIX/BNIP3-dependent mitophagy, thereby mitigating ROS-induced nuclear genomic instability and delaying tumor initiation (64). The tumor suppressor p53 has been shown to enhance mitophagy by transcriptionally activating DNA damage-regulated autophagy modulator 1, facilitating the removal of dysfunctional mitochondria and inducing apoptosis in premalignant cells, as validated in colorectal precancerous models (65,66). Furthermore, excessive mitochondrial damage can trigger 'autosis', a form of autophagic cell death, via mitochondrial membrane potential collapse and ATP depletion, irreversibly eliminating premalignant cells. In inflammation-associated carcinogenesis, mitophagy is proposed to block chronic inflammation-driven tumorigenesis by clearing mitochondrial damage-associated molecular patterns (such as cardiolipin and mtDNA), thereby inhibiting NLRP3 inflammasome activation and IL-1β secretion (67). Critically, the tumor-suppressive effects of mitophagy are context- and stage-dependent: Activation of mitophagy in PTEN-deficient or KRAS-mutant precancerous models reduces hyperproliferative lesions, whereas the same intervention in advanced tumors may paradoxically promote malignancy due to metabolic rewiring and survival adaptation. This spatiotemporal duality underscores the necessity of stage-specific targeting of mitophagy pathways in cancer therapy (68,69).

EC-specific regulation of mitophagy. Emerging evidence highlights stage- and molecular context-specific regulation of mitophagy in EC, although research in this field remains sparse (70). Dysregulation of the PTEN/PI3K/AKT pathway, observed in >80% of EC cases, impairs PINK1/Parkin-mediated mitophagy, resulting in the accumulation of dysfunctional mitochondria, increased ROS levels, heightened genomic instability and estrogen-driven proliferation (71). However, evidence has revealed that PTEN-deficient EC cells activate an alternative mitophagy pathway mediated by the autophagy and beclin 1 regulator 1-autophagy-related protein 5 complex, which bypasses Unc-51 like autophagy activating kinase 1 (ULK1) inhibition and maintains mitochondrial quality control under mTORC1 hyperactivation (13). In type I EC, hyperactivated mTORC1 phosphorylates ULK1 at Ser757, disrupting the ULK1-AMP-activated protein kinase (AMPK) complex essential for mitophagy initiation and promoting tumor cell survival (34). Notably, advanced TP53-mutant ECs exhibit hypoxia-driven compensatory upregulation of BNIP3L/NIX-mediated mitophagy, which is transcriptionally activated by HIF-1α under hypoxic conditions to sustain mitochondrial metabolism and chemoresistance, thereby contributing to the poor prognosis of p53-aberrant tumors (33). This dual regulatory role, tumor-suppressive in early stages and pro-tumorigenic in advanced disease, underscores the need for stage-specific therapeutic strategies. Restoring PINK1/Parkin signaling in PTEN-deficient models may improve mitochondrial quality control, while targeting BNIP3L/NIX in TP53-mutant tumors could enhance chemosensitivity. However, the molecular mechanisms underlying these context-dependent effects require further elucidation.

In conclusion, mitophagy serves as both a 'metabolic accomplice' and a 'genomic custodian' in EC, with its

dualistic role underscoring the therapeutic conundrum in targeting mitochondrial quality control. The transition from tumor-suppressive to pro-survival functions is intricately linked to disease stage, molecular subtypes (such as POLE-mutated and TP53-aberrant) and metabolic rewiring driven by PTEN/PI3K dysregulation or obesity-associated stress (33). Future endeavors must prioritize stage-adaptive strategies, activating mitophagy to enforce genomic fidelity in precancerous lesions while inhibiting FUNDC1/PINK1/Parkin-driven pathways to disrupt metabolic plasticity in advanced tumors. Integrating multi-omics profiling (such as mitophagic flux mapping and spatial metabolomics) with clinical staging will unlock context-specific vulnerabilities, enabling the design of precision therapies that convert mitophagy from a foe to an ally in the battle against EC, as illustrated in Fig. 1.

4. Regulatory network of ferroptosis in EC

Core mechanisms and resistance pathways of ferroptosis. Ferroptosis is an iron-dependent RCD pathway that is driven by lipid peroxidation, originating from redox imbalance, dysregulated lipid metabolism and disrupted iron homeostasis (72); however, cellular adaptation to these stressors hinges on dynamic modifications of core regulatory pathways, which paradoxically form the molecular basis of ferroptosis resistance (29). The GPX4/GSH axis is a central defense system: System Xc^- [composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2] imports cystine for GSH synthesis and GPX4 utilizes GSH to reduce lipid peroxides. Resistance often arises from GPX4 or System Xc^- upregulation (73). Alternatively, the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 (CoQ10) axis has been identified as a key GPX4-independent pathway wherein FSP1 reduces ubiquinone to ubiquinol, which quenches lipid radicals (28). Acyl-CoA synthetase long-chain family member 4 (ACSL4) is a well-established promoter of ferroptosis that enriches membranes with polyunsaturated fatty acids; its suppression diminishes ferroptosis sensitivity (74). Iron metabolism serves a dual role: Iron overload amplifies lipid peroxidation, while iron storage proteins [such as ferritin heavy chain 1 (FTH1)] buffer toxicity. The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is a recognized suppressor of ferroptosis, primarily by activating antioxidant genes (such as GPX4 and FTH1) (29,75). p53 exerts context-dependent effects, which may include inhibiting SLC7A11 or activating spermidine/spermine N1-acetyltransferase 1 (65-67).

Ferroptosis in EC progression. Ferroptosis exhibits a dynamically regulated dual role in EC progression: Its suppressed state drives tumor invasion, metastasis and therapy resistance through multifaceted molecular mechanisms, while ferroptosis-inducing strategies have the potential to reverse drug resistance and inhibit metastasis (16,76-78). The core regulatory hubs GPX4 and Nrf2 are upregulated in EC and are functionally synergistic. GPX4 maintains membrane stability by reducing toxic lipid peroxides (such as phosphatidylethanolamine hydroperoxide), whereas Nrf2 enhances antioxidant defense via transcriptional activation of SLC7A11 (cystine/glutamate antiporter) and FTH1 (iron storage protein) (79-81). A multivariate analysis of the TCGA-uterine corpus endometrial carcinoma cohort revealed that GPX4/Nrf2 co-upregulation was independently associated with lymph node metastasis risk [odds ratio (OR), 3.21; 95% confidence interval (CI), 1.38-7.45; P=0.007] and International Federation of Gynecology and Obstetrics III/IV staging (OR, 2.94; P=0.012) (82,83). EC cells evade ferroptosis through epigenetic reprogramming, including the microRNA (miR)-424-5p-mediated destabilization of ACSL4 mRNA via 3'untranslated region binding (validated by dual-luciferase assays) and hypermethylation of the ACSL4 promoter CpG island (methylation β-value >0.6; P<0.001), collectively suppressing pro-ferroptotic lipid peroxidation (83). Iron metabolism dysregulation exacerbates malignant phenotypes: FTH1 upregulation reduces the labile iron pool by enhancing iron storage, thereby inhibiting Fenton reaction-driven lipid peroxidation, while divalent metal transporter 1 mediates lysosomal iron efflux to amplify ferroptosis sensitivity in metastatic niches. Concurrently, transferrin receptor 1 (TFR1)-mediated iron overload activates pro-angiogenic factors (such as VEGF) via the mitochondrial ROS/HIF-1α axis (84). Clinical translational studies have highlighted the therapeutic potential of combining erastin with cisplatin: Cisplatin-resistant EC cells (Ishikawa-CR line) acquire ferroptosis resistance via GPX4/FSP1 dual-pathway upregulation, whereas erastin/cisplatin co-treatment induces caspase-3-independent cell death (4.2-fold apoptosis increase; P<0.001) (11,85). Metformin suppresses SLC7A11 transcription via the AMPK/p53 axis (chromatin immunoprecipitation-quantitative PCR-validated), reducing peritoneal metastases by 68% in patient-derived xenograft (PDX) models (P=0.002) (86,87). Interim analysis of the NCT04817332 phase II trial demonstrated improved objective response rates with erastin/carboplatin-paclitaxel combination therapy in recurrent EC (51 vs. 32% for monotherapy; P=0.039), albeit with increased ferroptosis-related toxicity (grade 3 anemia, 28 vs. 12%) (88). Parallel preclinical investigations provided complementary insights: To further elucidate the cellular diversity underlying treatment responses, single-cell RNA sequencing of patient-derived EC samples revealed significant heterogeneity in ferroptosis-related gene expression profiles. Meanwhile, leveraging nanodelivery systems to encapsulate ferroptosis inducers has been established as a promising strategy in preclinical models to enhance tumor selectivity and reduce systemic toxicity (89). These findings systematically elucidate the pivotal role of ferroptosis dysregulation in EC progression and provide novel directions for developing redox metabolism-targeted precision therapies (16).

5. Dynamic regulation of oxidative stress as an integrative hub

Crosstalk between mitophagy and ferroptosis. ROS serve as key signaling molecules that dynamically coordinate the balance between mitophagy and ferroptosis. Mitochondrial ROS promote PINK1/Parkin-mediated mitophagy, which clears damaged mitochondria and limits lipid peroxidation (31,52). Conversely, endoplasmic reticulum-derived ROS activate the inositol-requiring enzyme 1α/c-Jun N-terminal kinase pathway, upregulating ACSL4 to enhance membrane polyunsaturated fatty acid incorporation and ferroptosis sensitivity (90). Lipid peroxidation products [such as phospholipid

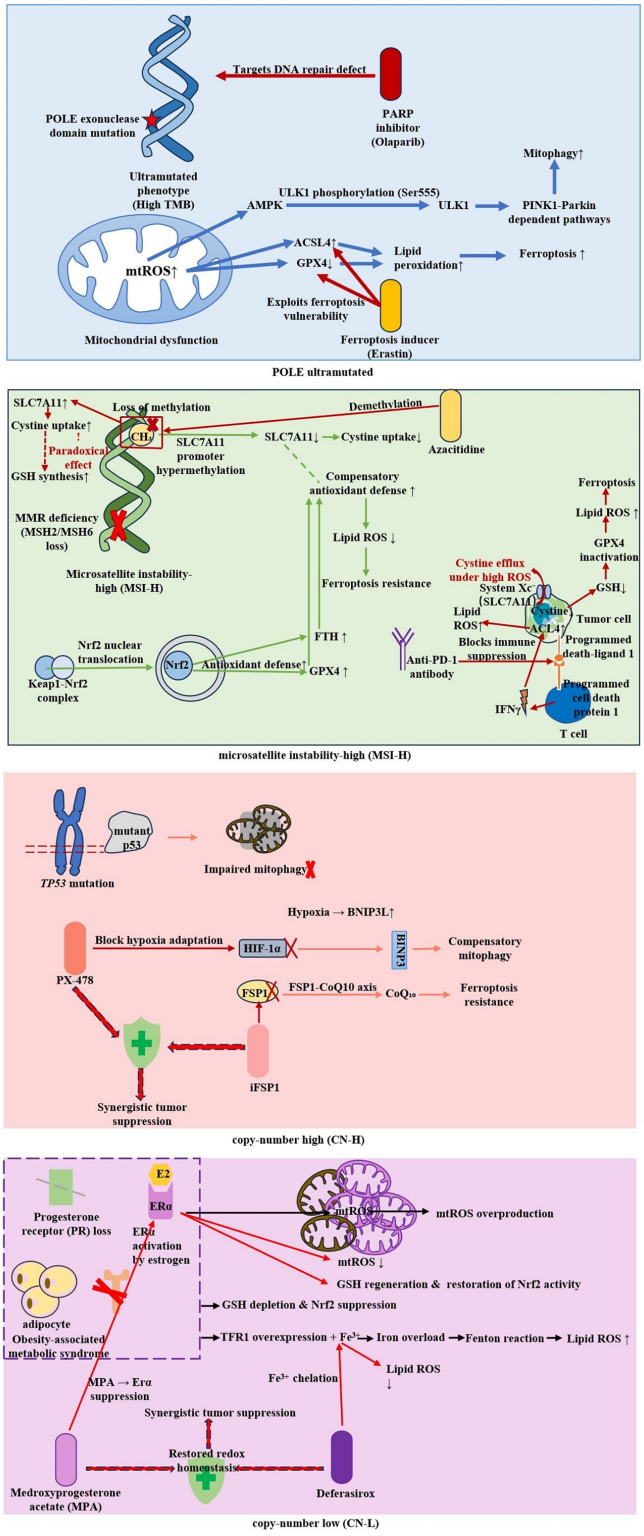

Figure 1. Schematic illustration of the design of precision therapies for The Cancer Genome Atlas molecular subtypes of endometrial cancer, depicted by targeted inhibitors acting on their respective molecular pathways within each subtype panel. These subtypes exhibit distinct redox adaptations and associated therapeutic vulnerabilities. The POLE-mutated subtype exhibits synthetic lethality to PARP inhibitors and heightened ferroptosis sensitivity. The MSI-H subtype exhibits SLC7A11 hypermethylation, conferring sensitivity to demethylating agents. The CN-H subtype exhibits TP53-mutant-driven HIF-1α stabilization and FSP1 upregulation, vulnerable to HIF-1α and FSP1 co-inhibition. The CN-L subtype displays ERα-driven oxidative stress and Nrf2 suppression, targetable by iron chelators. CN-H, copy-number high; CN-L, copy-number low; ERα, estrogen receptor α; FSP1, ferroptosis suppressor protein 1; HIF-1α, hypoxia-inducible factor-1α; MSI-H, microsatellite instability-high; Nrf2, nuclear factor erythroid 2-related factor 2; PARP, poly (ADP-ribose) polymerase; POLE, DNA polymerase ε; SLC7A11, solute carrier family 7 member 11; AMPK, AMP-activated protein kinase; NOXs, NADPH oxidases; keap1, Kelch-like ECH-associated protein 1; NADPH, nicotinamide adenine dinucleotide phosphate; Cat, catalase; PRX, peroxiredoxin; SOD2, superoxide dismutase 2; FTH1, ferritin heavy chain 1; TFR, transferrin receptor; STEAP3, six-transmembrane epithelial antigen of the prostate 3; IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; IMS, mitochondrial intermembrane space; ECT, mitochondrial electron transport chain; LPCAT3, lysophosphatidylcholine acyltransferase 3; ALOXs, arachidonate lipoxygenases; LOXs, lipoxygenases; PUFA, polyunsaturated fatty acid; PUFA-PL-OOH, PUFA-containing phospholipid hydroperoxide; TXNRD1, thioredoxin reductase 1; GSH, glutathione; GPX, GSH peroxidase; GSR, GSH disulfide reductase; GSSG, oxidized GSH; LC3, microtubule-associated protein 1A/1B-light chain 3.

hydroperoxides (PLOOH)] further amplify mitochondrial damage, establishing a feedforward loop (91). This interplay exhibits concentration dependence in EC: Physiological ROS levels promote cytoprotective mitophagy via AMPK-ULK1 signaling to suppress early malignant transformation (92), whereas chemotherapy (such as cisplatin)-induced ROS trigger ferroptosis-dominated cell death by depleting GSH and inhibiting GPX4 (93). A previous study has revealed that estrogen receptor α (ERα) activation in EC cells simultaneously upregulates mitochondrial ROS production and autophagy-related genes (such as BNIP3), driving dynamic imbalances between mitophagy and ferroptosis to fuel tumor progression (94).

Mitophagy and ferroptosis are interconnected through shared molecular nodes, forming a bidirectional regulatory network (95). On the one hand, mitophagy suppresses ferroptosis by degrading ACSL4, a key enzyme that catalyzes polyunsaturated fatty acid-phospholipid synthesis, and removing lipid peroxidation precursors (96). On the other hand, ferroptosis-derived lipid peroxides (such as PLOOH) activate PINK1/Parkin or NIX/BNIP3L-dependent mitophagy via mitochondrial membrane oxidation (97). Emerging evidence demonstrates that ACSL4, a ferroptosis-specific regulator, induces mitochondrial Ca^{2+} overload, leading to membrane depolarization and subsequent mitophagy initiation (98). Additionally, labile iron released during ferroptosis exacerbates mitochondrial oxidative damage through Fenton reactions, creating an 'iron-ROS-mitophagy' cycle. In EC, PTEN loss-induced dysregulation of the PI3K/AKT/mTOR pathway disrupts redox homeostasis via dual mechanisms: Impairing ULK1 phosphorylation to block protective mitophagy and downregulating GPX4 to heighten ferroptosis susceptibility (33). Combined targeting of both pathways (for example, using mitophagy inducer urolithin A + ferroptosis activator RSL3) synergistically inhibits tumor growth in preclinical models, highlighting the therapeutic potential of modulating the ROS-mitophagy-ferroptosis axis (16,71), as illustrated in Fig. 2.

Pathological disruption of redox homeostasis. EC is characterized by alterations in redox homeostasis that is driven by hormonal imbalances and somatic mutations. Estrogen dominance, a hallmark of type I EC, activates ERα-mediated mitochondrial biogenesis, amplifying superoxide generation while epigenetically suppressing Nrf2-dependent antioxidant defenses through promoter hypermethylation of NFE2 like bZIP transcription factor 2 (NFE2L2) (99). Conversely, progesterone exerts protective effects by binding to the progesterone receptor-B isoform, upregulating thioredoxin reductase and GSH synthetase through cAMP-response element binding protein phosphorylation, a mechanism disrupted in obesity-associated progesterone resistance (100). PTEN loss (occurring in 40-80% of cases) exacerbates this imbalance via dual pathways: i) Hyperactivation of PI3K/AKT/mTORC1 inhibits ULK1-driven mitophagy, allowing the accumulation of ROS-generated damaged mitochondria; and ii) transcriptional repression of the FSP1/CoQ10 axis through yes-associated protein and transcriptional coactivator with PDZ-binding motif nuclear translocation, sensitizing cells to ferroptosis (101,102). Single-cell multi-omics has identified PTEN-null CD44-positive aldehyde dehydrogenase 1 family member A1-high cancer stem cells (CSCs) that evade ferroptosis via aldehyde detoxification and CoQ10 recycling, establishing a redox-buffered niche resistant to oxidative stress (103).

Redox adaptations exhibit temporal evolution during disease progression: i) Premalignant lesions exhibit compensatory upregulation of mitophagic machinery (elevated Parkin RBR E3 ubiquitin-protein ligase and BNIP3 levels) with concomitant suppression of ferroptosis drivers (low ACSL4 expression); ii) early invasive tumors activate the FSP1/CoQ10 antioxidant system and suppress mitophagy through mTORC1-mediated transcription factor EB phosphorylation, resulting in lipid peroxide accumulation; and iii) advanced tumors undergo metabolic rewiring (glutamine-driven oxidative phosphorylation and HIF-1α signaling) to enforce mitophagy dependency and ferroptosis resistance (104-106). These stage-specific adaptations inform rational therapeutic targeting: mTOR inhibition with rapamycin restores protective mitophagy in premalignant states, while FSP1 inhibitors combined with ferroptosis inducers (such as imidazole ketone erastin) overcome therapy resistance in advanced disease.

Network integration of core regulatory nodes

Dynamic regulation of the Nrf2/Kelch-like ECH-associated protein 1 (Keap1) axis and EC-specific dysregulation. The Nrf2/Keap1 pathway serves as a central hub for oxidative stress responses, integrating antioxidant defenses, mitophagy and ferroptosis to maintain cellular homeostasis. Under physiological conditions, Keap1-mediated ubiquitination and degradation of Nrf2 restrict its activity, while oxidative stress triggers Nrf2 nuclear translocation, activating target genes such as heme oxygenase 1 (which degrades pro-ferroptotic labile iron) and SQSTM1/p62 (which promotes clearance of damaged mitochondria via selective autophagy) (107). In EC, KEAP1 loss-of-function mutations or NFE2L2 (encoding Nrf2) amplifications lead to constitutive Nrf2 activation, driving p62-dependent mitophagy and suppressing ferroptosis to favor tumor survival. Estrogen enhances NFE2L2 transcription via ERα binding to its promoter, while progesterone upregulates Keap1 expression through PR-B, establishing hormone-dependent oscillations in Nrf2 activity (100,108). Furthermore, Nrf2-hyperactive tumors reprogram metabolism by upregulating glutaminase and the cystine transporter xCT/SLC7A11, sustaining mitochondrial function and ferroptosis resistance, a mechanism particularly prominent in PTEN-deficient subtypes (13).

Iron-sulfur (Fe-S) cluster metabolism as a therapeutic nexus. Fe-S cluster biogenesis acts as a critical node linking mitochondrial integrity and ferroptosis sensitivity. Deficiencies in mitochondrial Fe-S assembly systems [such as iron-sulfur cluster assembly enzyme (ISCU) and frataxin] disrupt electron transport chain function, causing superoxide accumulation and PINK1/Parkin-mediated mitophagy, while cytosolic labile iron pool expansion exacerbates lipid peroxidation via Fenton reactions, increasing ferroptosis susceptibility (109). In EC, ISCU promoter hypermethylation and miR-214 upregulation synergistically impair Fe-S cluster synthesis, whereas cancer-associated fibroblasts rescue redox homeostasis by delivering Fe-S complementation factors (such as cysteine desulfurase) via exosomes (110,111). Therapeutic Fe-S

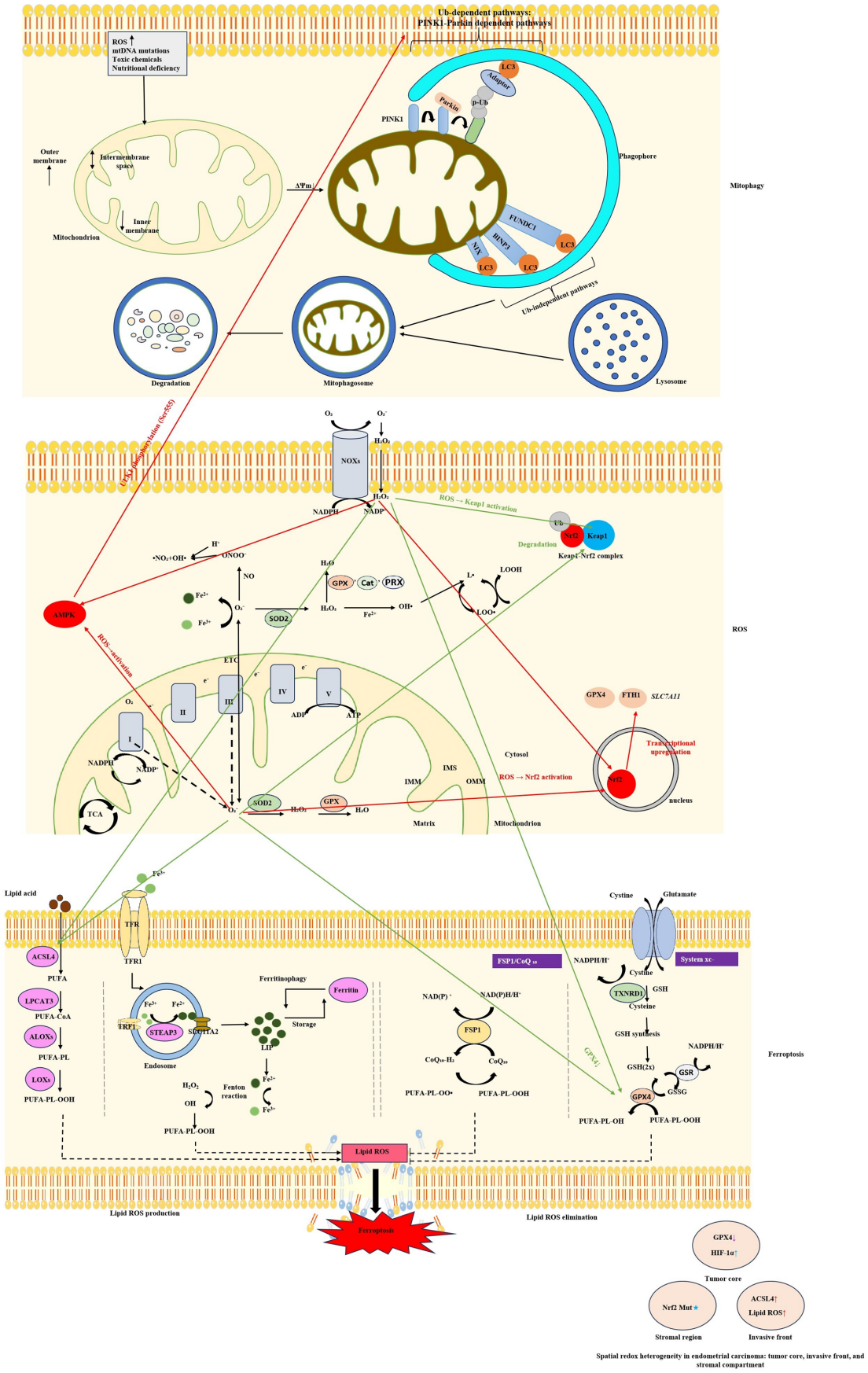

Figure 2. A conceptual model of the mitophagy-ferroptosis crosstalk in endometrial cancer, revealing nodes for potential combined therapeutic targeting. Mitophagic clearance of damaged mitochondria modulates cellular ROS levels. Low ROS levels promote Nrf2-mediated antioxidant defense and ferroptosis resistance, while high ROS levels suppress Nrf2 and facilitate ferroptosis execution via ACSL4 and Fenton reactions. Key molecular players (PINK1/Parkin, FUNDC1, GPX4 and FSP1) form a critical regulatory network. Spatial tumor heterogeneity in EC is also summarized. ACSL4, acyl-CoA synthetase long-chain family member 4; EC, endometrial cancer; FSP1, ferroptosis suppressor protein 1; FUNDC1, FUN14 domain-containing protein 1; GPX4, glutathione peroxidase 4; Nrf2, nuclear factor erythroid 2-related factor 2; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species.

cluster donors (such as Fe_4S_4) restore mitochondrial function while inducing ferroptosis, exhibiting synergistic efficacy in PTEN-deficient organoid models and offering a novel strategy to overcome therapy resistance (103).

Spatiotemporal dynamics of oxidative stress regulation. The spatiotemporal dynamics of oxidative stress critically influence therapeutic responses in EC. Chemotherapy (e.g., cisplatin) induces biphasic ROS generation (112): Acute-phase mitochondrial ROS activate AMPK-ULK1-mediated protective mitophagy, promoting cell survival, while chronic-phase ROS accumulation triggers ferroptosis via GSH depletion and GPX4 inactivation. The circadian regulators BMAL1 and CLOCK rhythmically control the expression of autophagy genes like LC3B. This regulation drives a peak in autophagic activity at night, which helps to counteract the oxidative damage that accumulates during the day (113). Chronotherapy strategies leveraging these rhythms [e.g., administering ferroptosis inducers (such as erastin) during active circadian phases] synergize with endogenous ROS fluctuations, enhancing treatment efficacy (114,115).

Spatial heterogeneity further shapes oxidative stress regulation: Hypoxic tumor cores suppress ferroptosis via HIF-1α-mediated downregulation of ACSL4 and TFR1, while upregulating BNIP3-driven mitophagy to maintain CSC stemness. By contrast, high-ROS microenvironments at invasive fronts activate NF-κB/STAT3 signaling to promote EMT and FSP1/CoQ10-dependent ferroptosis resistance (112,116). CSCs remodel stromal niches via exosomal transfer of antioxidants (such as glutathione S-transferase P1) and iron chelators, creating localized 'oxidative sanctuaries' (117). Nanotherapeutic strategies exploiting this heterogeneity, such as ROS-responsive carriers delivering autophagy inhibitors to cores and ferroptosis inducers to invasive fronts, exhibit potent antitumor effects in preclinical models (118).

In summary, the spatiotemporal regulation of oxidative stress defines distinct therapeutic vulnerabilities, enabling chronotherapeutic and microenvironment-targeted interventions.

Translational implications. The oxidative stress network offers novel biomarkers and therapeutic strategies (119). Combined evaluation of mitophagy (for example, mtDNA copy number) and ferroptosis markers (for example, lipid peroxidation products) enables real-time monitoring of tumor redox status (120). $CD8^+$ T cell-derived IFNγ enhances ferroptosis susceptibility via STAT1/interferon regulatory factor 1/ACSL4 signaling, suggesting synergies between immune checkpoint inhibitors and ferroptosis inducers (121). Advanced imaging technologies (such as nanoprobe-based iron tracking) integrated with artificial intelligence (AI) algorithms accurately predict ferroptosis sensitivity (122).

Spatiotemporally optimized combinations, such as sequential autophagy inhibition followed by ferroptosis induction, overcome compensatory resistance (123,124). ROS-responsive nanocarriers achieve precise drug release by exploiting microenvironmental features (such as low pH and high GSH levels), effectively targeting both hypoxic cores and invasive fronts. Additionally, targeting PTEN-null vulnerabilities with mTOR and glutaminase inhibitors synergistically blocks mitophagy and induces ferroptosis, achieving remarkable responses in patient-derived models (101).

These advances highlight the clinical potential of targeting oxidative stress dynamics for precision therapy in EC.

Current challenges and future directions. Key challenges remain in modeling oxidative stress dynamics. Current organoid systems lack spatiotemporal resolution for tumor-microenvironment crosstalk (for example, immune cell interactions and hormone gradients) (125). Integrating single-cell transcriptomics with spatial metabolomics is essential to resolve redox heterogeneity and niche-specific adaptations (126,127). Mechanistic gaps persist regarding the subcellular localization of ferroptosis regulators (such as FSP1) and the crosstalk between Nrf2 and circadian pathways (96-99). Compensatory activation, such as GPX4 inhibition upregulating FSP1/CoQ10, requires sequential targeting strategies tailored to tumor heterogeneity (128-131). AI-driven drug discovery (for example, using deep generative models) predicts synergistic combinations (such as mTOR inhibitors with ferroptosis inducers), validated in PDX models (132).

Future studies must integrate computational biology and high-resolution omics to map the oxidative stress landscape, enabling personalized therapeutic strategies.

6. Knowledge gaps and translational barriers

The establishment of oxidative stress as a nexus between mitophagy and ferroptosis unveils a novel therapeutic landscape in EC (95,120,133). However, clinical translation is impeded by defined knowledge gaps and practical challenges that must be prioritized in future research.

Unresolved mechanistic and immunological questions. A primary unresolved question is the spatiotemporal dynamics of this interplay within the tumor microenvironment (TME). The precise thresholds of oxidative stress that dictate a switch from pro-survival mitophagy to lethal ferroptosis across different molecular subtypes and disease stages remain unmapped (120). This context-dependent duality necessitates a deeper understanding of how metabolic and hormonal cues influence this balance. Concurrently, the immunological consequences of targeting this axis constitute a critical knowledge gap. It is not known whether ferroptosis induction or mitophagy modulation can enhance antitumor immunity by, for example, triggering immunogenic cell death or reversing immunosuppressive niches, which would create a rationale for combinations with immunotherapy.

Clinical trial landscape and practical hurdles. The compelling preclinical evidence stands in stark contrast to the current clinical trial landscape, highlighting a significant translation gap. To definitively assess the clinical translation of these mechanisms, a systematic search of the ClinicalTrials.gov registry (https://clinicaltrials.gov/) was conducted on September 10, 2025. The search strategy utilized keywords including 'endometrial cancer', 'ferroptosis', 'mitophagy' and related terms. Crucially, the following exclusion criteria were applied: i) Trials not focused on EC; ii) non-interventional studies; and iii) trials where direct targeting of mitophagy

or induction of ferroptosis was not an explicit primary strategy. It is important to note that this search constituted a systematic search of trial registries and not a systematic review; as such, a formal quality assessment of the identified trials or a synthesis of data from existing publications was not performed, which is a limitation of this methodological approach.

This rigorous search confirmed a complete absence of clinical trials specifically designed to directly target mitophagy or induce ferroptosis as a primary therapeutic strategy in EC. However, the search identified several interventional trials investigating agents with indirect mechanistic links to these pathways: i) mTOR inhibitors: Active and completed trials investigating everolimus (such as NCT01797523 and NCT00870337) are relevant due to the established role of mTOR signaling in regulating the mitophagic flux and cellular stress responses; and ii) AMPK activators: Multiple trials involving metformin (such as NCT04576104, NCT07145827 and NCT01205672) are of interest based on preclinical evidence suggesting its potential to modulate AMPK activity and sensitize cells to ferroptosis.

The absence of direct-targeting trials underscores the nascent stage of translating these concepts into clinical applications. Conversely, the prevalence of trials involving mTOR inhibitors and AMPK activators suggests a growing clinical recognition of the importance of targeting broader metabolic and stress-response pathways in EC, which may indirectly influence mitophagy and ferroptosis (134,135).

Translation of these insights faces significant barriers. The lack of robust, dynamic biomarkers (such as circulating lipid peroxidation products) beyond static molecular classification severely hinders patient stratification. Furthermore, managing systemic toxicity, particularly of potent ferroptosis inducers, is a paramount concern. Overcoming this requires the development of advanced nano-theranostic platforms engineered for EC-specific targeting [e.g., against folate receptor α (FRα)] and TME-responsive drug release (e.g., triggered by high ROS levels) to maximize efficacy and minimize off-target effects. The inherent compensatory activation of parallel pathways (such as upregulation of the FSP1/CoQ10 axis upon GPX4 inhibition) further necessitates the rational design of combination therapies.

7. Precision medicine perspectives and conclusion

In summary, the present review consolidates evidence that oxidative stress functions as a critical mechanistic nexus coordinating mitophagy and ferroptosis in EC. The deregulation of this axis presents a compelling therapeutic vulnerability.

The future of targeting this nexus lies in precision medicine strategies that directly address the aforementioned challenges, with tailored approaches for both mitophagy and ferroptosis: i) Biomarker-guided stratification: Future efforts must integrate functional redox biomarkers with molecular subtyping to identify patient populations most likely to benefit, such as those with PTEN-deficient tumors exhibiting heightened ferroptosis sensitivity. For mitophagy, this necessitates stage-aware strategies, such as activating it to enforce genomic fidelity in precancerous/early-stage lesions (such as PTEN-deficient) while inhibiting its pro-survival function in advanced or therapy-resistant tumors (such as TP53-mutant or BNIP3L/NIX-high). ii) Intelligent therapeutic platforms: The development of stimuli-responsive nanocarriers is indispensable to overcome the dual challenges of drug delivery efficiency and systemic toxicity, enabling spatially controlled therapy within the TME for ferroptosis inducers. Complementary efforts should develop mitochondrially-targeted delivery systems for mitophagy modulators (such as PINK1 activators or FUNDC1 inhibitors) to achieve organelle-specific precision. iii) Rational combination therapies: Overcoming adaptive resistance necessitates 'two-pronged' strategies, such as co-inhibiting parallel defense pathways (for example, GPX4 and FSP1) or combining ferroptosis inducers with immunotherapy in appropriate subtypes (such as MSI-H) to exploit immunogenic cell death. Similarly, mitophagy inhibition can be rationally combined with standard chemo-/radiotherapy to prevent treatment resistance or with ferroptosis inducers to synergistically disrupt mitochondrial metabolism and redox homeostasis.

By addressing the knowledge gaps and embracing these precision approaches, the transformative potential of targeting the oxidative stress-mitophagy-ferroptosis axis can be realized, paving the way for novel and effective management strategies in EC.

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Authors' contributions

FL designed the study and critically revised the manuscript. QY wrote the initial draft of the manuscript. LR performed analysis and interpretation of the underlying data to draw the figures and authored and revised the figure legends and the corresponding part of the Methods section. FR participated in the revision of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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