The role of autophagy in fibrosis: Mechanisms, progression and therapeutic potential (Review)

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Abstract. Various forms of tissue damage can lead to fibrosis, an abnormal reparative reaction. In the industrialized countries, 45% of deaths are attributable to fibrotic disorders. Autophagy is a highly preserved process. Lysosomes break down organelles and cytoplasmic components during autophagy. The cytoplasm is cleared of pathogens and dysfunctional organelles, and its constituent components are recycled. With the growing body of research on autophagy, it is becoming clear that autophagy and its associated mechanisms may have a role in the development of numerous fibrotic disorders. However, a comprehensive understanding of autophagy in fibrosis is still lacking and the progression of fibrotic disease has not yet been thoroughly investigated in relation to autophagy-associated processes. The present review focused on the latest findings and most comprehensive understanding of macrophage autophagy, endoplasmic reticulum stress-mediated autophagy and autophagy-mediated endothelial-to-mesenchymal transition in the initiation, progression and treatment of fibrosis. The article also discusses treatment strategies for fibrotic diseases and highlights recent developments in autophagy-targeted therapies.

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Abbreviations: AM, alveolar macrophage; AMPK, adenosine monophosphate-activated protein kinase; ATG, autophagy-related proteins; CMA, chaperone-mediated autophagy; CS, crystalline silica; EC, endothelial cell; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EndMT, endothelial mesenchymal transition; ERS, endoplasmic reticulum stress; FIP200, FAK family interacting protein of 200 kDa; GAP, GTPase-activating protein; IM, interstitial macrophage; IPF, idiopathic pulmonary fibrosis; LC3, microtubule-associated protein 1A/1B-light chain 3; LC3-I, the cytosolic form of LC3; LC3-II, the conjugate form of LC3-I with phosphatidylethanolamine; LEC, lymphatic endothelial cell; mTOR1, mammalian target of rapamycin 1; mTORC1, mechanistic target of rapamycin complex 1; PF, pulmonary fibrosis; RHEB, Ras homolog enriched in brain; ROS, reactive oxygen species; SIRT1, sirtuin 1; TSC, tuberous sclerosis complex; ULK1, unc51-like kinase 1; PERK, protein kinase RNA-like endoplasmic reticulum kinase; UPR, unfolded protein response; VPS34, vacuolar protein sorting 34; AGEs, advanced glycosylation end-products; ATF6, activating transcription factor 6; FOX, forkhead box; IRE1, inositol-requiring enzyme 1; FAM172A, family with sequence similarity 172, member A; MFG-E8, milk fat globule-egf factor 8; PE, phosphatidylethanolamine; RAGE, AGE receptor; TCEP, tris(2-chloroethyl) phosphate; TFEB, transcription factor EB

Key words: autophagy, fibrosis, macrophage autophagy, endoplasmic reticulum stress, endothelial mesenchymal transition

Contents

1. Introduction

Fibrosis can occur in a variety of organs. Several tissues and organs have been found to be affected by fibrosis in clinical practice, including the liver, kidney, lung, heart and skin (1,2). The global annual incidence of fibrosis-related diseases is ~1 in 20, affecting nearly a quarter of the world's population and causing a substantial disease burden (3). Human health is seriously threatened by fibrotic diseases. The diverse structural characteristics and microenvironments of different organs and tissues in the human body contribute to discrepancies in the fibrosis process (4). Despite the growing research on fibrosis, the portrayal of the mechanisms of fibrosis remains incomplete. There are still many questions that need to be continuously discussed, so developing targeted therapies for fibrotic diseases remains challenging.

Autophagy, also known as type II programmed cell death, is a dynamic biological process in which cells utilize lysosomes to selectively remove damaged, aged or excess biomolecules and organelles, thereby releasing free small molecules for cellular recycling and utilization. It is regarded

as an essential mechanism for the body's self-protection (5). Almost all eukaryotic cells demonstrate a basal level of autophagy.

Recent research confirms that autophagy is critical to fibrotic disease progression (6,7). Autophagy can affect fibrosis through various pathways. For instance, macrophage autophagy could inhibit fibrosis progression, while endoplasmic reticulum stress (ERS) may promote fibrosis progression by impacting autophagy (8-10). Furthermore, autophagy has a crucial role in the progression of fibrotic diseases by mediating endothelial-mesenchymal transition (EndMT) (11). Autophagy can also have an impact on fibrotic disease development by prompting cells to produce secretory phenotypes and regulating the secretion of inflammatory factors. Increasing evidence suggests that autophagy-related processes can affect the initiation and progression of fibrosis, which can assist in driving the development of antifibrotic medicines based on inhibiting or promoting autophagy. In this review, the different roles of autophagy during fibrosis progression and the potential of autophagy and autophagy-related processes as therapeutic targets for fibrosis were dissected and discussed.

2. Autophagy

Classification of autophagy. Microautophagy, chaperone-mediated autophagy (CMA) and macroautophagy are the three forms of autophagy in mammalian cells. In spite of the differences among the three types of autophagy, the basic functions and features are merging with cargo at the lysosome for degradation and recycling (12,13). Microautophagy involves lysosomes directly engulfing cytoplasmic components, mainly smaller organelles within the cell. Microautophagy can be either selective or non-selective, is capable of degrading entire organelles and can be activated by signals such as environmental stress. The main function of microautophagy is to remove dysfunctional intracellular proteins and organelles (13-15). CMA utilizes heat shock proteins and transporter proteins on the lysosomal membrane to degrade proteins expressing targeting motifs. Molecular chaperones such as heat shock protein family A (Hsp70) member 8/HCS70 recognize the targeting motif and transfer the protein to the lysosomal membrane. At the lysosomal membrane, the target binds to lysosomal-associated membrane protein (LAMP)-2A on the lysosome and is subsequently transferred to the lysosomal lumen for degradation (13,16). Macroautophagy is the most common form of autophagy. Macroautophagy primarily targets larger organelles, removing intracellular waste and damaged organelles. The central process of macroautophagy involves the formation of autophagosomes by the encapsulation of lipid membrane structures around the substrates designated for degradation. Autophagosomes fuse with lysosomes to form autolysosomes after the phagocytosis of cytoplasmic material. Thus, the substrate undergoes degradation (13,17).

The process of autophagy. Autophagy is a dynamic and complex process (if not specified, the form of autophagy discussed in this paper refers to macroautophagy). The macroautophagy process can be summarized in four steps: Initiation, autophagosome formation, autophagolysosome formation and autophagolysosomal degradation (18). i) Autophagy initiation: This stage comprises the generation and expansion of phagocytic vesicles. This step involves two protein complexes: The vacuolar protein sorting 34 (VPS34) complex [VPS34, BECLIN1, autophagy-related 14 (ATG14) and VPS15] and the Unc51-like kinase 1 (ULK1) complex (19). ii) Autophagosome formation: During this process, phagocytic vesicle expansion occurs, and two ubiquitin-like binding systems regulate the expansion and completion of autophagosomes: The ATG12-ATG5-ATG16L system and the ATG8/microtubule-associated protein 1A/1B-light chain 3 (LC3) system (18). Ubiquitin-like system ATG12-ATG5-ATG16L: ATG16L interacts with ATG5-ATG12 to form ATG5-ATG12-ATG16L, which adheres to autophagosomes and participates in the extension of autophagic precursor membranes (20,21). ATG8/LC3 ubiquitin-like system: LC3 is ATG8's mammalian homologue, and ATG4 cleaves it into cytoplasmic LC3-I (the cytosolic form of LC3). During the formation of autophagosomes, cytosolic LC3-I participates in ubiquitin-like reactions through interactions with ATG7 and ATG3 and then couples with phosphatidylethanolamine (PE) to generate lipidated LC3-II (the conjugate form of LC3-I with PE). As an autophagosome structural protein, LC3-II is attached to the membrane of autophagosomes. Subsequently, ATG4 excises LC3-II from the outer membrane of autophagic lysosomes during the autophagic degradation process, and the generated product, LC3-I, can be recycled. In autophagic lysosomes, LC3-II on the inner membrane, along with encapsulated content, is degraded by lysosomes (22). Unlike ATG5-ATG12-ATG16L, LC3B-II is distributed on both the outer and inner surfaces of autophagosomes. LC3B-II is essential for the extension and completion of autophagic membranes. After autophagosome membrane closure, the ATG16-ATG5-ATG12 complex detaches from the vesicle, but part of LC3B-II still covalently binds to the membrane. Thus, LC3B-II is currently the most widely recognized molecular marker (21,23). iii) Autophagy lysosome formation: After autophagosome formation, LC3-II on the outer membrane is removed from the PE by ATG4 and liberated back into the cytoplasm (24). LAMP, the lysosomal membrane protein, and RAB7, a small GTPase, are crucial in the fusion processes of autophagosomes and lysosomes. This process is characterized by the formation of isolated membrane structures containing cytoplasmic constituents (25). Furthermore, acetylation plays a significant role in autophagic lysosome biogenesis (26). iv) Autophagolysosomal degradation: The inner membrane of the autophagosome is degraded by lysosomal enzymes during autophagic lysosome formation so that the contents of the two are well mixed. As the contents continue to degrade, raw materials necessary for cellular life activities, such as amino acids, are continuously produced, which are conveyed to the cytosol to be re-utilized by the cell, whereas residues that cannot be recycled may be expelled from the cell or retained in the cytosol (27).

Regulation of autophagy. Several forms of cellular stress can activate autophagy [including, but not limited to, DNA damage, protein aggregates, intracellular pathogens, reactive oxygen species (ROS), hypoxia, damaged organelles and nutrient or growth factor deficiencies]. This process involves the promotion or inhibition of multiple signaling pathways to coordinate the various stages of autophagy (28). Autophagy

is regulated by three major nutrient-sensing pathways: The mammalian target of rapamycin complex 1 (mTORC1) pathway, the adenosine monophosphate-activated protein kinase (AMPK) pathway and the oxidized nicotinamide adenine dinucleotide-dependent histone deacetylase sirtuin 1 (SIRT1) pathway (29).

The mTORC1 pathway. The mammalian target of rapamycin 1 (mTOR1), a serine/threonine protein kinase, is a member of the PI3K-associated kinase family and is sensitive to rapamycin (30). mTORC1 phosphorylates ULK1 and ATG13 to inactivate the autophagy regulatory complex composed of ULK1, ATG13, FAK family interacting protein of 200 kDa (FIP200) and ATG101, which affects autophagy vesicle formation. Under nutrient-rich conditions, mTORC1 inhibits autophagy-promoting kinase activity of the ULK1 complex by mediating site-specific phosphorylation of ULK1 and ATG13. However, there are adaptive changes in how the organism is regulated during starvation and cellular stress, such as mTORC1 inhibition and ULK1 dissociation from mTORC1. Consequently, site-specific phosphorylation of ULK1 and ATG13 is deregulated (19). Meanwhile, the autophosphorylation of threonine located at site 180 activates the ULK1 complex, and in this state, ULK1 phosphorylates ATG13, FIP200 and ATG101 in the ULK1 complex. After that, the active ULK1 complexes are transferred to the isolation membrane of the endoplasmic reticulum, thereby initiating autophagy (31,32). Furthermore, AMPK affects mTORC1 as well. In the presence of sufficient glucose, active mTORC1 inhibits ULK1 activation in two mechanisms: Phosphorylating the ULK1-specific site (serine 757) and disrupting the ULK1 and AMPK interaction. After ULK1 activation is inhibited, autophagy initiation is also impaired. In the presence of glucose insufficiency, AMPK activity inhibits the phosphorylation of mTORC1, then ULK1 interacts with AMPK and is phosphorylated, resulting in ULK1 activation and autophagy initiation (31). In the class III phosphatidylinositol 3-kinase complex I, the phosphorylation of ATG14, autophagy and beclin 1 regulator 1 (AMBRA1) and nuclear receptor binding factor 2 (NRBF2) inhibits the nucleation step of autophagy. However, mTORC1 regulates autophagy by phosphorylating ATG14, AMBRA1 and NRBF2 (25). A study showed that mTORC1 regulates the elongation process in autophagosome formation and influences LC3 binding to the autophagosome membrane through targeting WD repeat domain, phosphoinositide interacting 2 (WIPI2) and P300 acetyltransferases, respectively. For instance, activating P300 by inhibiting its intramolecular autoinhibition promotes the acetylation of LC3, depriving it of the ability to be lapidated (33). By binding to ATG16L, WIPI2 promotes the binding of ATG12-ATG5-ATG16L complexes to phagophores, therefore enhancing lipidation of LC3 by PE (34). In addition to directly inhibiting autophagy, mTORC1 can also indirectly inhibit it by regulating the transcription of genes associated with lysosomal biogenesis. For instance, recent research on transcription factor EB (TFEB) has found that TFEB regulates the expression of genes involved in lysosomal biogenesis and autophagy, including those associated with autophagosome formation, fusion of autophagosomes with lysosomes, and lysosomal biogenesis (35). In addition, overexpression of TFEB increased the expression of UV radiation resistance associated, WIPI, microtubule-associated protein 1 light chain 3B, sequestosome 1, VPS11, VPS19 and ATG9B, which are involved in various steps of autophagy (36). Furthermore, mTORC2 can also play multiple roles as an important regulator in autophagy regulation, including the indirect inhibition of autophagy through the activation of mTORC1 (37). In summary, mTOR inhibits autophagy induction. Therefore, the development of novel mTOR inhibitors that can precisely regulate autophagy provides new avenues for the treatment of clinically difficult diseases (Fig. 1).

The AMPK pathway. In the cell, AMPK acts as an energy sensor, actively upregulating catabolism and inhibiting anabolism (38). By specifically phosphorylating different autophagy-associated protein complexes or different components of the same protein, AMPK can affect different phases of autophagy and thus promote autophagy (39). AMPK antagonizes mTORC1 to regulate the activity of the ULK complex. Two distinct mechanisms induce autophagy when AMPK is activated: Inhibition of mTOR and direct phosphorylation of ULK1 (40). Most regulatory factors can affect mTORC1 by interfering with tuberous sclerosis complex (TSC) and ras homolog enriched in brain (RHEB). RHEB binds to GTP to form RHEB-GTP, which then binds and activates mTORC1. The TSC complex, however, has GTPase activity that hydrolyzes GTP to inactivate RHEB-GDP. Therefore, the TSC complex can inhibit mTORC1 activity by modulating RHEB (41). AMPK is phosphorylated and activated under low-energy conditions or starvation situations, and it inhibits mTOR activity in two ways. i) AMPK directly phosphorylates TSC2, promoting GTPase-activating protein (GAP) activity in the TSC complex. GTP dephosphorylation of RHEB-GTP results in its conversion to the inactive RHEB-GDP, which interrupts RHEB-mediated mTORC1 activation. ii) AMPK inhibits the mTOR signaling pathway by directly phosphorylating regulatory associated protein of mTOR complex 1 (RAPTOR), stopping RAPTOR from binding to mTOR or its substrates (35,37). The inactivation of mTOR leads to decreased ULK1 phosphorylation and increased ULK1 binding to AMPK, thereby exhibiting a unique role in autophagy regulation. AMPK promotes the activity of ULK1, which induces autophagy during glucose deprivation. AMPK interacts with the serine/proline-rich region of ULK1 and directly phosphorylates ULK1 at several sites, resulting in changes in the conformation of ULK1. The conformational changes in ULK1 enhance interactions between ULK1 and the other components of the ULK1 complex, increasing its activity and stability. mTORC1 regulates the interactions between AMPK and ULK1 through various mechanisms. In the nutrient-rich environment, ULK1 is phosphorylated by mTORC1, inhibiting its interaction with AMPK (42,43). In addition to this, mTORC1 can also phosphorylate ATG13, which decreases ULK1 complex activity. In contrast, under starvation conditions, mTORC1 activity is inhibited, leading to the rapid dephosphorylation of ULK1 and ATG13, which activates ULK1 kinase and initiates autophagy. Accompanying this change is that AMPK and ULK1 interact more effectively, increasing ULK1 activity and promoting ULK1-ATG13-FIP200 complex formation (30). Thus, AMPK and mTORC1 coordinately regulate ULK1 to induce autophagy in response to cellular nutrient levels. AMPK, ULK1 and mTORC1 form a signaling triad that constitutes a transient feedback mechanism to maintain the

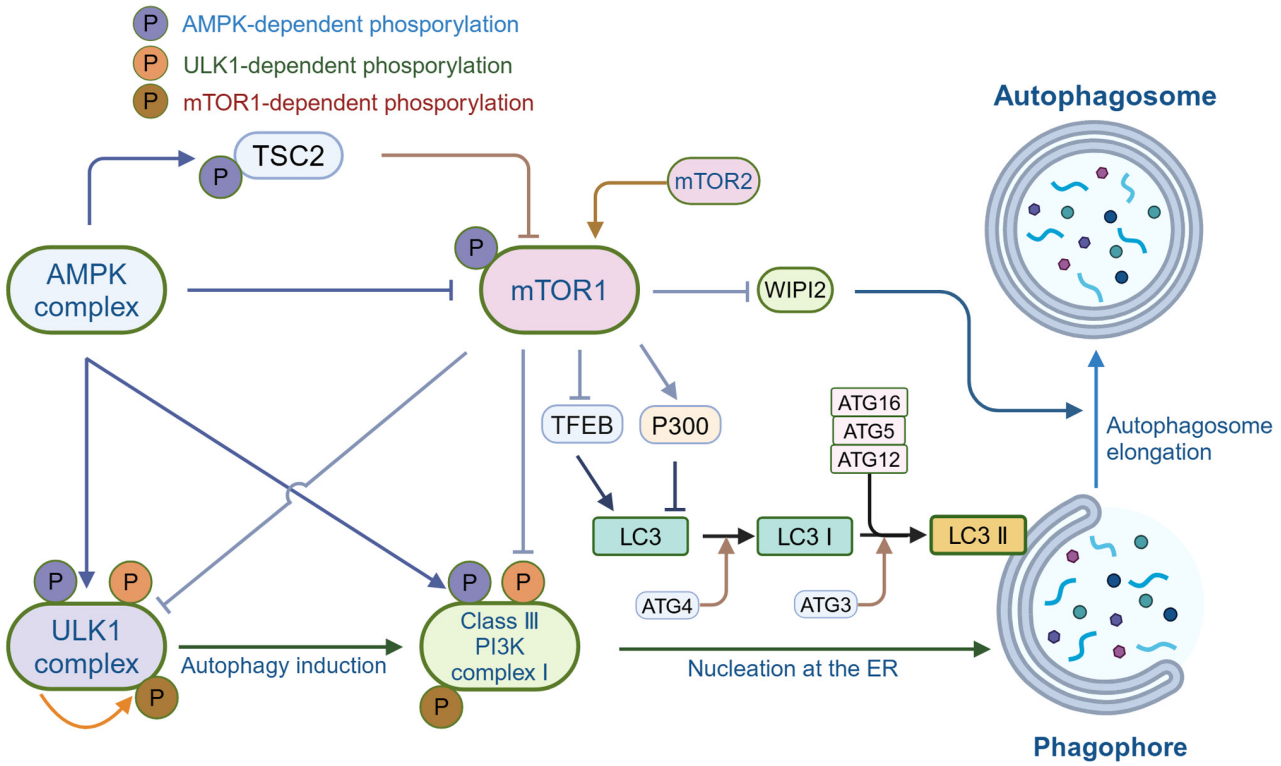

Figure 1. Regulation of autophagy by mTORC1 and AMPK. AMPK and mTORC1 collaboratively regulate ULK1 to induce autophagy in response to cellular nutrient levels. AMPK activation inhibits mTORC1 phosphorylation and promotes ULK1 phosphorylation, and activated ULK1 initiates autophagy. Reduced mTORC1 activity dephosphorylates ULK1, thereby activating the ULK1 complex to initiate autophagy. AMPK inhibits mTORC1 activation by directly phosphorylating TSC2. AMPK can directly phosphorylate mTOR1, thereby inhibiting the mTOR signaling pathway. mTORC1 can affect autophagy by directly regulating class III phosphatidylinositol 3-kinase complex I activity. mTORC1 can participate in the regulation of autophagosome formation through TFEB, WIPI2 and p300. ATG, autophagy-related proteins; AMPK, adenosine monophosphate-activated protein kinase; ER, endoplasmic reticulum; LC3, microtubule-associated protein 1A/1B-light chain 3; LC3-I, the cytosolic form of LC3; LC3-II, the conjugate form of LC3-I with phosphatidylethanolamine; mTORC1, mechanistic target of rapamycin complex 1; TSC, tuberous sclerosis complex; ULK1, unc51-like kinase 1.

dynamic homeostasis of autophagy (44). AMPK also affects autophagy by regulating the activity of the PI3KC-3/VPS34 complex and the transcriptional regulation of autophagy (45) (Fig. 1).

The SIRT1 pathway. SIRT1, an NAD^+-dependent multifunctional enzyme, acts as a regulator of autophagy (46). In mammals, there are seven different SIRT isoforms. Although all SIRTs possess NAD^+-dependent catalytic structural domains, their localizations and functions differ due to the different lengths and sequences between their C- and N-terminals. Among mammalian SIRTs, SIRT1 shares close homology with the yeast Sir2 and is one of the most thoroughly studied SIRTs (47,48). SIRT1 is distributed in the nucleus and cytoplasm, where it primarily functions by deacetylating various histones and non-histone proteins and thus participates in the regulation of a variety of cellular processes, such as cell proliferation, differentiation, autophagy and cell survival (49). Under conditions of hunger or nutrient deprivation, the body experiences energy deprivation, leading to elevated intracellular NAD^+ levels that activate SIRT1 (50-52). Thus, SIRT1 is able to sense the energy status of the cell and adapt to energy deprivation by regulating autophagy (50,52). The mechanism by which SIRT1 regulates autophagy is as follows. i) SIRT1 directly deacetylates autophagy-related proteins to promote autophagy (52,53). ii) SIRT1 deacetylates and activates transcription factors to enhance autophagic activity (54). iii) SIRT1 inhibits mTOR, hence facilitating the autophagic process (55). iv) SIRT1 activates autophagy to degrade damaged or excess organelles and proteins (56). Afterwards, the cell recycles metabolites such as amino acids and fatty acids for use in times of hunger or nutrient deprivation, thereby maintaining cell homeostasis and energy balance (56). Thus, SIRT1 activates autophagy during hunger or nutrient deprivation through multiple mechanisms, which not only helps cells to remove damage and maintain metabolic homeostasis, but also optimizes energy utilization and enhances cellular viability. SIRT1 regulates autophagy through its deacetylase activity and mediates it by associating with the various steps of autophagy, including initiation, elongation, maturation, fusion and degradation (49,57,58). SIRT1 acts by regulating TSC2 stability during autophagy initiation (59). TSC2 inactivates the mTORC1 signaling pathway by inhibiting the RHEB, which results in the activation of mTORC1. RHEB requires GTP to activate mTORC1; however, the GAP structural domain of TSC2 is capable of stimulating GTP hydrolysis (58,60). Increased TSC2 stabilization increases GTP hydrolysis, which accelerates the inactivation of RHEB. These changes downregulate mTOR signaling and initiate autophagy (58,60). Under hypoxic conditions, SIRT1 mediates autophagy initiation through regulating BNIP3. SIRT1 deacetylates forkhead box (FOX)O3, enabling it to bind to the BNIP3 promoter and induce BNIP3 expression (61,62). BNIP3 can act

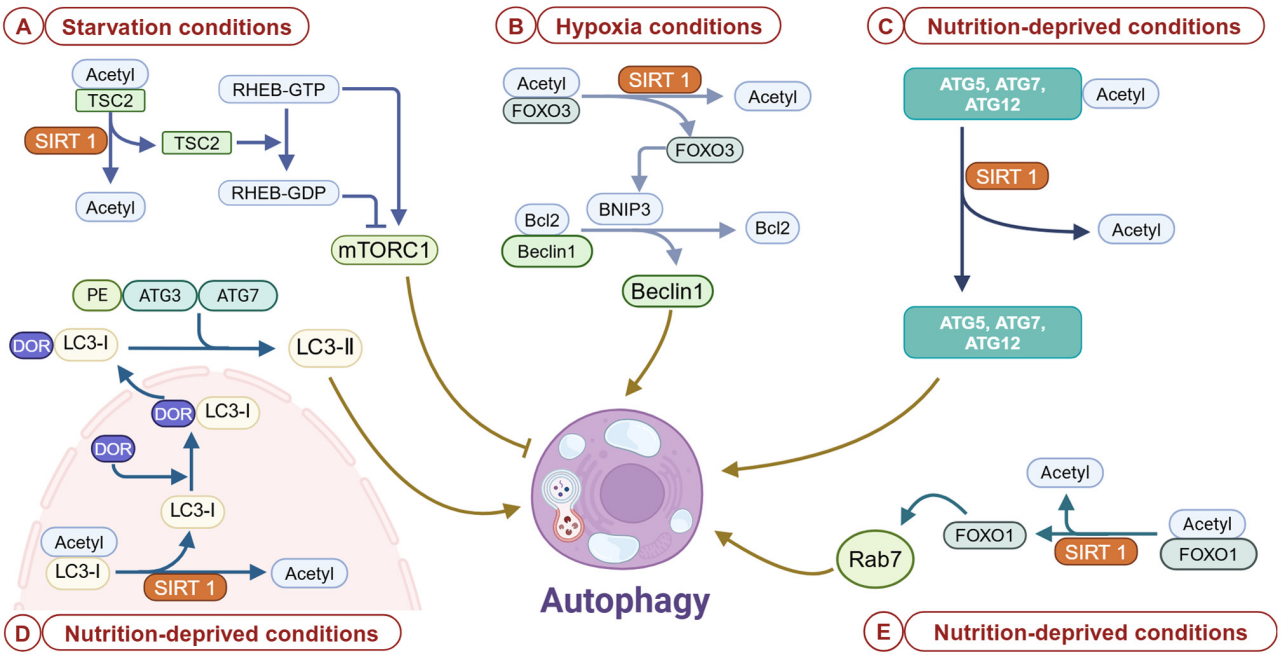

Figure 2. Regulation of autophagy by SIRT1. SIRT1 is a deacetylase that plays a regulatory role in autophagy through its deacetylation activity. (A) Under starvation conditions, In the presence of SIRT1, TSC2 stability is elevated through deacetylation, turning RHEB-GTP into RHEB-GDP, which downregulates mTOR signaling and initiates autophagy. (B) Under hypoxia conditions, after deacetylation of FOXO3 by SIRT1, FOXO3 binds to BNIP-3 and promotes the expression of BNIP-3. BNIP-3 dissociates Bcl-2 from Beclin1, thereby initiating autophagy. (C) Under nutrition-deprived conditions, SIRT1 deacetylates ATG5, ATG7 and ATG12, promoting the formation of the ATG16-ATG5-ATG12, which contributes to the elongation of autophagic vesicles and initiates autophagy. (D) Under nutrition-deprived conditions, SIRT1 deacetylates nuclear LC3-I. Nuclear LC3-I is translocated to the cytoplasm through interaction with DOR proteins. In the cytoplasm, LC3-I further transformed into LC3-II, which activates autophagy. (E) Under nutrition-deprived conditions, SIRT1 deacetylates FOXO1, which promotes Rab7 expression and initiates autophagy. ATG, autophagy-related proteins; DOR, tumor protein p53 inducible nuclear protein 2; LC3, microtubule-associated protein 1A/1B-light chain 3; LC3-I, the cytosolic form of LC3; LC3-II, the conjugate form of LC3-I with phosphatidylethanolamine; mTORC1, mechanistic target of rapamycin complex 1; PE, phosphatidylethanolamine; RHEB, Ras homolog enriched in brain; SIRT1, sirtuin 1; TSC, tuberous sclerosis complex.

on the Bcl-2-Beclin1 complex to dissociate Beclin1 from it, thereby increasing the concentration of Beclin1, which further triggers autophagy (63). The deacetylase function of SIRT1 also regulates the elongation and maturation phases. Under nutrient-rich conditions, EP300, an E1A-binding protein P300 acetyltransferase, inhibits ATG16-ATG5-ATG12 complex formation by acetylating ATG5, ATG7 and ATG12, which prevents autophagosome elongation (64). By contrast, in times of nutrient deprivation or starvation, SIRT1 deacetylates ATG5, ATG7 and ATG12 directly, which contributes to the formation of the ATG16-ATG5-ATG12 complex, thereby enhancing autophagic vesicle elongation (65). The SIRT1 protein also regulates the translocation of the LC3-I protein from the nucleus to the cytoplasm, which contributes to autophagy. Under nutrient starvation, nuclear LC3-I, after deacetylation by SIRT1, interacts with tumor protein p53 inducible nuclear protein 2 to move LC3-I from the nucleus to the cytoplasm. Deacetylated cytoplasmic LC3-I binds to PE by interacting with ATG7 and ultimately forms LC3-II (62,66). During the fusion and degradation of autophagosomes with lysosomes, RAB7, as a Ras-related GTP-binding protein, functions to facilitate autolysosome formation by facilitating autophagosome translocation to lysosomes (67). Under nutrient starvation, SIRT1 deacetylates FOXO1 and increases RAB7 expression (68). The interaction between SIRT1 and autophagy is bidirectional. On the one hand, SIRT1 can regulate autophagic activity; on the other hand, autophagy also controls the level of SIRT1 by affecting lysosomal degradation (69). Early autophagosome formation is fundamental and critical for the initiation of the overall autophagic response (70). Therefore, the mechanism by which SIRT1 acts in the early stages of autophagy is even more important for the regulation of autophagy (Fig. 2).

The functions of autophagy. During the process of growth and development, autophagy is an essential catabolic process for basic biological activities (71). According to current research findings, the functions of autophagy include the following: i) Immune Response: Autophagy removes intracellular pathogens, such as viruses and bacteria, through a process called heterophagy. It also regulates inflammation and antigen presentation, contributing to the normal function of the immune system (72). ii) Nutrient recycling: In times of nutrient deprivation or starvation, the autophagic process recycles cellular components and provides nutrients to cells. In degrading and recycling cytoplasmic material, autophagy provides cells with vital components, such as amino acids, for survival and energy production (56). iii) Energy homeostasis: During periods of metabolic stress, such as fasting or exercise, autophagy is upregulated to provide a source of energy by breaking down cellular components. As a result, cells adapt to changing nutrient supplies and maintain a balance of energy (56). iv) Development and differentiation: Autophagy participates in various differentiation and developmental processes, including cellular differentiation, tissue

remodeling and embryonic development. It helps to remove unnecessary or excessive cellular components, shape tissues and organs, and promote normal cell development and differentiation (73,74). v) Cellular quality control: Autophagy sustains cellular homeostasis by cleaning out damaged or dysfunctional cellular components (e.g., misfolded proteins, damaged organelles and excess or aggregated proteins). By eliminating these components, autophagy contributes to preventing the accumulation of toxic substances and maintaining cellular homeostasis (75).

3. Fibrotic diseases

Fibrosis is defined as the over-accumulation of extracellular matrix (ECM) components in organs or tissues, which is a normal and necessary stage in the process of organ or tissue repair (76). However, continual or severe injury causes the accumulation of ECM components, which can disrupt tissue structural integrity, lead to organ dysfunction and ultimately cause various organ failures (76). Fibrosis affects almost every tissue in an organism, including the skin, lungs, liver, kidneys and ligamentum flavum (77,78).

The core mechanisms of fibrosis. Numerous different triggers can contribute to the ongoing aggravation of progressive fibrosis disease. However, regardless of the initiating event, all fibrotic diseases are characterized by the activation of ECM-producing myofibroblasts, which are the primary mediators of fibrotic tissue remodeling (76,78). When tissues are injured, myofibroblasts from various sources remodel the extracellular environment to initiate healing responses, which restore tissue integrity and promote the replacement of parenchymal cells (79). Typically, the deposition of ECM proteins in the initial stages of tissue healing contributes to the tissue repair process. In mild injuries, the fibrotic matrix is taken up during the tissue repair process (80). However, sustained injury can lead to dysregulation of this process, resulting in excessive deposition of ECM proteins, myofibroblast activity and the gradual development of a chronic inflammatory environment infiltrated by macrophages and immune cells (81). In such a microenvironment, cells are exposed to a significant release of cytokines and growth factors by myofibroblasts, such as TGF-β and WNT1, which are significant players in the fibrotic process (82). TGF-β and WNT1 bind to their stem cell surface receptors and initiate downstream signaling, ultimately leading to nuclear translocation of SMAD2/3 and CREB binding protein/β-catenin transcriptional regulators. This leads to the upregulation of target gene expression, further enhancing myofibroblast differentiation and the production and secretion of ECM proteins, such as collagen, laminin and fibronectin (83,84). As excess ECM deposition proceeds, the matrix undergoes structural changes and hardens (76). Cells sense ECM tension through mechanotransduction of cell surface integrin receptors, which activate the Hippo signaling pathway and its major downstream effectors Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) (85). In addition, activated YAP and TAZ translocate to the nucleus and promote the upregulation of pro-growth genes, such as connective tissue growth factor and platelet-derived growth factor, which promote myofibroblast proliferation and activation through the PI3K/AKT/mTOR pathway (85).

Biomarkers of fibrotic diseases. In clinical practice, biomarkers of fibrotic diseases are crucial for early diagnosis, disease progression tracking, prognostic evaluation and treatment efficacy assessment (86). The following are generic fibrosis markers in fibrotic diseases. i) Collagen: The main component of fibrosis, as well as its degradation products in serum, can be used as markers (87,88). ii) Fibronectin: An important component of the ECM, upregulated during fibrosis (89). iii) Matrix metalloproteinases and their inhibitors: They reflect matrix remodeling processes, balancing the disintegration and accumulation of the ECM, and serve a crucial role in regulating fibrosis (90-92). iv) MicroRNAs: MicroRNAs regulate the expression of fibrosis-related genes in a variety of fibrotic diseases and have potential diagnostic and therapeutic value (93-95).

Biomarkers of fibrotic disease exhibit considerable variability across different tissues and organs. Liver fibrosis markers include the following: i) The aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio, which is often elevated in liver fibrosis (96); ii) fibrosis indices: AST to platelet ratio index (based on AST level and platelet count) and FIB-4 (based on age, AST, ALT and platelet count) (97); iii) FibroTest: A score is calculated in combination with various serum markers (e.g., α2-microglobulin, apolipoprotein-A1, transferrin, total bilirubin, γ-glutamyltransferase, etc.) and is used to assess the degree of liver fibrosis (98); iv) hyaluronic acid: Serum levels of hyaluronic acid are significantly elevated during liver fibrosis (99). Pulmonary fibrosis markers include the following: i) Krebs von den Lungen-6 (KL-6): KL-6, released after damage to alveolar epithelial cells, is commonly used in the monitoring of idiopathic pulmonary fibrosis (100-102); and ii) surfactant protein D, which reflects lung tissue damage and the inflammatory state (102-104). Renal fibrosis markers include i) Neutrophil gelatinase-associated lipocalin, which is elevated in acute kidney injury and renal fibrosis (105); and ii) urinary collagen degradation products, which reflect collagen metabolism and fibrotic activity (106,107). Cardiac fibrosis markers include i) Galectin-3, which is involved in the fibrotic process and it is an important marker of cardiac fibrosis (108-110); ii) ST2 protein, which reflects cardiac stress and fibrotic activity with significant prognostic value (109,110); and iii) collagen degradation products, reflecting cardiac collagen metabolism (111).

The mechanism of fibrosis varies among organs, so the selection of appropriate markers needs to be tailored to the specific type of disease.

4. Autophagy-related pathways in fibrotic diseases

Macrophage autophagy, macrophage polarization and fibrosis. Macrophages are immune cells found in almost all tissues. Macrophages participate in non-specific immunoregulation by phagocytosis of bacteria and other pathogens, while also transmitting signals to lymphocytes to participate in specific immunoregulation, thus contributing to immunity, repair and homeostasis of the body (112). Macrophages may be categorized into two subpopulations, M1 and M2, which secrete pro-inflammatory and anti-inflammatory

factors, respectively (113). Continued research has indicated that macrophages play a critical role in regulating organ fibrosis (114). When an organ or tissue is infected or injured, macrophages polarize into the pro-inflammatory M1 phenotype, secreting proinflammatory cytokines to remove antigens and necrotic cells (115). Pro-inflammatory macrophages are categorized as M1-type macrophages, while anti-inflammatory macrophages are categorized as M2-type macrophages (115). During the organ or tissue repair phase, M2 macrophages secrete anti-inflammatory cytokines that suppress inflammation as well as contribute to tissue repair and remodeling (116). In a pathological situation, persistent pro-inflammatory macrophages produce pro-inflammatory factors continuously, resulting in chronic inflammation, which ultimately accelerates the progression of organ fibrosis significantly (117). It has been confirmed that autophagy regulates macrophage polarization (118). By inhibiting M1 proinflammatory macrophage polarization, macrophage autophagy ameliorates organ fibrosis and attenuates chronic inflammation (9).

After chronic or severe organ damage, fibrous connective tissue accumulates and parenchymal cells decrease, resulting in fibrosis. Continuous progression may result in severe damage to organ structure and function, or even death, posing a serious threat to human health and life (119). Pathologically, organ fibrosis is characterized by an imbalance in ECM homeostasis, resulting in excessive accumulation of collagen, fibronectin and other ECM components (120). Thus, fibrosis can also be seen as the result of abnormal tissue repair.

Pulmonary fibrosis (PF) is a common pathological feature and the ultimate outcome of numerous lung diseases. The main feature of PF is the excessive accumulation of ECM in the lungs, leading to the thickening of the alveolar walls, which ultimately causes the destruction of the alveolar structure and respiratory failure (121,122). Type II alveolar epithelial cell dysfunction or disorder is considered to be the initiating factor for PF. In addition, the contribution of macrophages in the evolution and progression of fibrotic diseases should not be overlooked (121,123). Depending on their location, macrophages in the lung are classified as alveolar macrophages (AMs) or interstitial macrophages (124). Normally, AMs reside in the alveolar cavity and are the most important component of the alveoli. AMs play a crucial role in preventing inflammation and fibrosis in the lungs.

In silicosis, autophagy inhibits inflammation and AM apoptosis and plays a protective role in the progression of silicosis. Du *et al* (125) found that crystalline silica (CS) triggered autophagy activity in AMs, thereby protecting AMs from CS-induced apoptosis. In AMs, diosgenin promoted autophagy and therefore attenuated CS-induced pulmonary fibrosis. Mechanistically, diosgenin can exert antifibrotic effects by enhancing macrophage autophagy activity. Diosgenin leads to mitochondrial dysfunction through silica inhalation and activates beclin1, which increases the expression of two key proteins of mitochondrial autophagy, PTEN-induced putative kinase 1 (PINK1) and parkin RBR E3 ubiquitin protein ligase (PARKIN), in AMs in mice. Diosgenin-mediated AMs mitochondrial autophagy eliminated damaged mitochondria and further ameliorated silicosis fibrosis. In ATG5 knockout mice, the protective effect of diosgenin was lost, and macrophages in these mice lacked autophagy function (126,127). In addition, microRNA-205-5p promotes macrophage autophagy by inhibiting S-phase kinase-associated protein 2-mediated ubiquitination of Beclin1, thereby suppressing lung fibrosis in silicosis mice (128). These experimental results suggest that tissue-resident macrophage autophagy can inhibit PF during silicosis progression. In addition, the lung has some macrophages of monocyte origin. The origin of these macrophages is different from that of tissue-resident macrophages. A study by Jessop *et al* (129) showed that in mouse monocyte-derived macrophages, exposure to CS can enhance autophagic activity. ATG5 gene knockout in mice resulted in impaired macrophage autophagy derived from monocytes, and more fibrosis was observed in ATG5 knockout mice exposed to silica compared to littermate control mice (129). These experimental results show that, similar to tissue-resident macrophages, monocyte-derived macrophages are also able to protect against CS-induced PF. In conclusion, macrophage autophagy has been shown to inhibit chronic inflammation, therefore inhibiting PF. However, there are different views among scientists, e.g., it has been suggested that autophagy may exacerbate lung injury and PF under certain circumstances, such as when autophagy levels are excessive or uncontrolled (130).

Renal fibrosis is the ultimate pathway leading to end-stage renal failure in almost all chronic progressive kidney diseases. In the kidney, macrophages play a crucial role in the generation and evolution of renal fibrosis (131). A study confirmed that macrophage autophagy suppresses the pro-inflammatory response of macrophages. Loss of macrophage autophagy leads to abnormal macrophage polarization, increased M1 and decreased M2, which causes worsening inflammation (132). Therefore, macrophage autophagy plays a crucial role in both macrophage polarization and suppressing inflammation. Liu *et al* (133) experimentally demonstrated that ubiquitin-specific peptidase 19 (USP19) can regulate NLR family pyrin domain containing 3 (NLRP3) function by affecting autophagy and thereby significantly influencing inflammation and macrophage polarization. In terms of mechanisms, USP19 increases autophagic flux and reduces mitochondrial ROS production, thus inhibiting inflammation and promoting macrophage polarization in M2 (133) (Fig. 3). In a study using two mouse models of experimental renal fibrosis, Bhatia *et al* (134) found that macrophage mitochondrial autophagy regulates the PINK1/mitofusin 2/PARKIN pathway, which could protect mice's kidneys from fibrosis (Fig. 3). Based on a renal fibrosis model, Zhang *et al* (135) found that fibrosis and macrophage infiltration were positively correlated with lymphangiogenesis. The activation of the VEGF-C/VEGFR3 signaling pathway inhibited macrophage autophagy, consequently facilitating macrophage M1 polarization, which then increased the transdifferentiation of M1 macrophages into lymphatic endothelial cells (LECs). By contrast, rapamycin-induced macrophage autophagy decreased M1 macrophage polarization and transdifferentiation to LECs. Thus, macrophage autophagy reduces LEC production, thereby inhibiting renal fibrosis (135). In summary, when the kidney is severely injured or repetitively injured, a large number of macrophages infiltrate into the damaged area and persist at the infiltration site, leading to chronic inflammation and renal fibrosis. Macrophage autophagy inhibits macrophage polarization to M1, thereby suppressing inflammation and renal fibrosis.

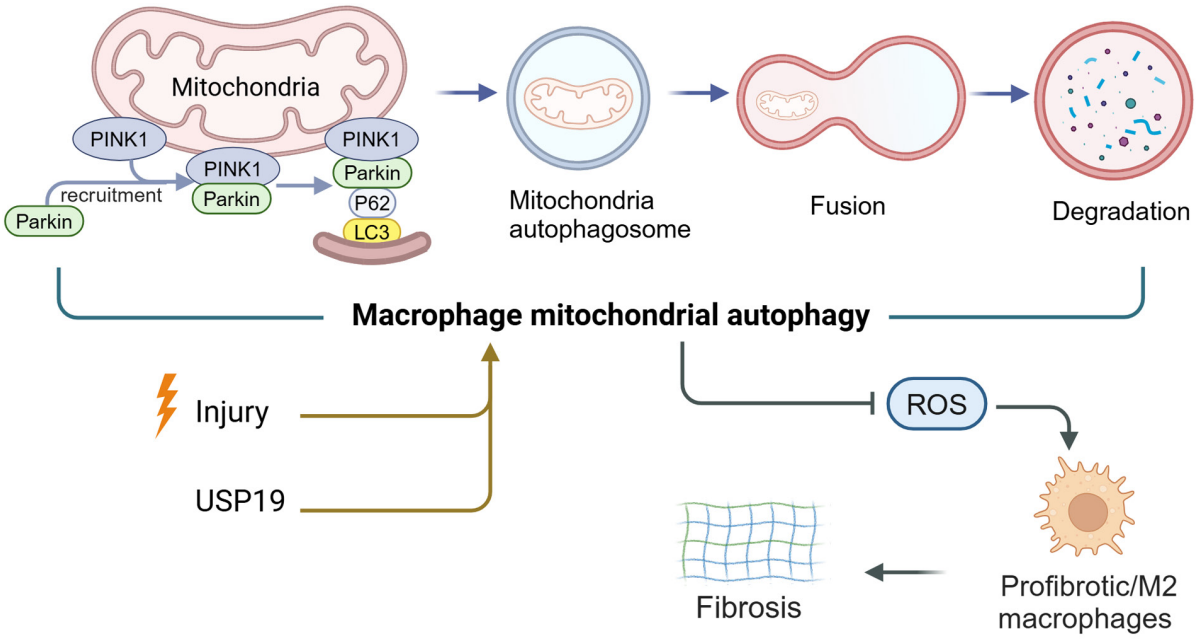

Figure 3. Impact of macrophage mitochondrial autophagy on fibrotic diseases. When mitochondrial injury occurs, PINK1 accumulates at the outer mitochondrial membrane, facilitating the recruitment and activation of Parkin. Parkin activation mediates ubiquitination of mitochondrial substrates and induces mitochondrial autophagy. Activated PINK1/Parkin can promote autophagic degradation of ubiquitinated proteins by mediating the attachment of ubiquitinated substrates to LC3 via specific ligand proteins (e.g., p62). The ubiquitinated mitochondria are engulfed by autophagosomes. After fusion of autophagosomes with lysosomes, lysosomal hydrolases are able to degrade autophagosomal contents. Macrophage mitochondria undergo autophagy through the PINK1-Parkin pathway. Mitochondrial autophagy inhibits ROS production in macrophages. ROS inhibit macrophage differentiation toward a pro-fibrotic/M2 phenotype, thereby reducing extracellular matrix accumulation and ameliorating fibrosis. LC3, microtubule-associated protein 1A/1B-light chain 3; ROS, reactive oxygen species; USP19, ubiquitin-specific protease 19; PINK1, PTEN-induced putative kinase 1.

In liver disease, macrophage autophagy similarly influences the progression of liver fibrosis. Lodder *et al* (136) demonstrated that the autophagic pathway in macrophages exerts a protective effect against hepatic fibrosis by limiting the release of inflammatory cytokines such as IL-1A and IL-1B from macrophages, which are key mediators of liver fibrosis. By contrast, rapamycin-induced autophagy activation limits the production of IL-1A and IL-1B in macrophages. These results reveal macrophage autophagy as a paracrine pathway that regulates IL-1-dependent activation of hepatic myofibroblasts.

In conclusion, macrophage autophagy protects against organ fibrosis.

ERS-induced autophagy and fibrosis. The endoplasmic reticulum, a complex and closed intracellular tubular endomembrane system interwoven into a three-dimensional network structure, is the central organelle responsible for the production of secreted and transmembrane proteins. The endoplasmic reticulum has the function of folding, assembling and modifying proteins (137). The biological functions of the endoplasmic reticulum are tightly regulated. Cellular homeostasis is disrupted when cells encounter various strong stimuli, such as nutritional deficiencies and oxidative stress stimuli, initiating a series of self-protective mechanisms, such as ERS (138). It has been indicated that ERS is activated when the folding capacity of the endoplasmic reticulum breaks down, resulting in accumulation of misfolded and unfolded proteins and disrupted protein homeostasis (139). In mammalian cells, three endoplasmic reticulum transmembrane proteins act as ERS sensors: Activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE1)α and protein kinase RNA-like endoplasmic reticulum kinase (PERK) (140,141) (Fig. 4). Under conditions of protein homeostasis, BIP (a molecular chaperone located in the endoplasmic reticulum membrane that facilitates degradation and refolding of unfolded and misfolded proteins accumulated in the endoplasmic reticulum to restore homeostasis) binds to these sensors, rendering them inactive (140,142). During ERS, BIP dissociates from the sensor (at this time, the affinity of BIP for unfolded and misfolded proteins increases), triggering the unfolded protein response (UPR), which is one of the adaptive responses to stress (141,143). Through activation of PERK, IRE1 and ATF6, the UPR promotes protein expression and restores the normal protein structure of misfolded or unfolded proteins. When the ERS-activated UPR is insufficient or does not completely eliminate the accumulated misfolded and unfolded proteins, as a complementary form, the ubiquitin-proteasome system collaborates with the UPR to degrade the misfolded and unfolded proteins, thus restoring the normal morphology of the endoplasmic reticulum (144). If the stimulus to the cell is persistent or excessively severe so that the synergistic action of the UPR and the ubiquitin-proteasome still does not fully restore the endoplasmic reticulum to its normal state, autophagy appears to be the last resort for restoring endoplasmic reticulum homeostasis. Persistence of ERS activates autophagy (145). Autophagy and ERS exhibit tight reciprocal regulation, both of which are crucial for maintaining cellular homeostasis and responding to environmental stimuli (146,147). The specific relationship includes the following four aspects: i) ERS induces autophagy: ERS

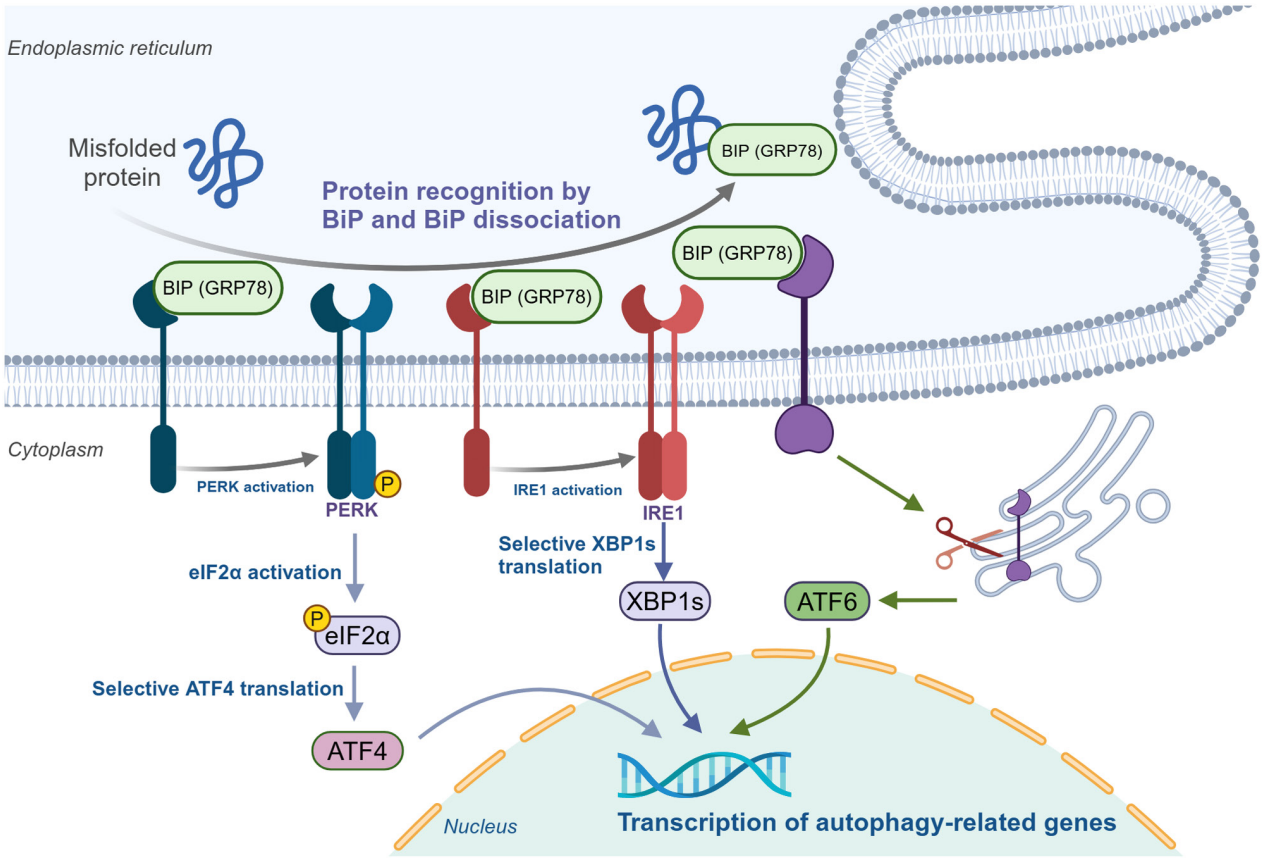

Figure 4. Impact of autophagy through endoplasmic reticulum stress. Upon recognition of the misfolded protein by BiP, it detaches from PERK, IRE1 and ATF6. ATF4, ATF6 and XBP1s subsequently produced in the cytoplasm translocate to the nucleus to promote the expression of autophagy-related genes. ATF, activating transcription factor; eIF2α, eukaryotic translation initiation factor 2 subunit alpha; IRE1, inositol-requiring enzyme 1; PERK, protein kinase RNA-like endoplasmic reticulum kinase; XBP1s, X-box binding protein 1s.

is triggered when unfolded or misfolded proteins accumulate in the endoplasmic reticulum. In response to this stress, cells initiate the UPR, and by activating sensors such as IRE1, PERK and ATF6, these UPR signaling pathways can facilitate the initiation of autophagy (146,148). ii) Autophagy to alleviate ERS: Autophagy can selectively degrade damaged endoplasmic reticulum regions, remove accumulated unfolded proteins and restore endoplasmic reticulum function (149). iii) Feedback regulation and homeostasis: A feedback regulatory mechanism exists between ERS and autophagy to ensure that cells balance survival and apoptotic signaling in response to stress (150,151). iv) Disease association: Dysregulated autophagy and ERS response are closely associated with the development of multiple diseases, e.g., PF (152), inflammatory bowel disease (147) and cardiovascular disease (153).

An association between ERS-induced autophagy and fibrotic disease has been identified. During fibrosis, autophagy regulates ERS to influence disease progression primarily through the following mechanisms: i) Reducing ERS load and modulating UPR: Autophagy reduces the endoplasmic reticulum burden and relieves ERS by breaking down aberrant proteins and damaged endoplasmic reticulum and activating the UPR, preventing further fibrosis development (154). ii) Modulation of inflammatory response: ERS is often accompanied by an inflammatory response, and autophagy can reduce tissue damage and the fibrosis process by removing inflammatory signaling molecules and inhibiting the excessive release of inflammatory mediators (147,155). iii) Maintaining cell survival and function: By regulating autophagy, cells can more effectively respond to protein folding stress, avoid apoptosis or necrosis, and protect the tissue structure (156,157). iv) Involvement in ECM metabolism: Autophagy indirectly affects fibrosis progression by regulating collagen degradation (154). Shu *et al* (158) demonstrated that ERS in renal proximal tubular cells can induce renal fibrosis. Furthermore, the PERK-mediated UPR signaling pathway links ERS to autophagy activation. Autophagy activation contributes, at least in part, to fibrosis associated with ERS (158). Xiong *et al* (159) found that cardiac Ca^{2+} concentrations increased and endoplasmic reticulum markers were upregulated during tris(2-chloroethyl) phosphate (TCEP)-induced cardiac fibrosis. However, Ca^{2+} overload and subsequent cardiac fibrosis were attenuated with the use of CDN1163, an inhibitor of the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase, which also suppressed the upregulation of endoplasmic reticulum markers. Furthermore, CDN1163 supplementation inhibited TCEP-induced excessive autophagy in the heart. Thus, by inhibiting sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase expression, TCEP can lead to Ca^{2+} overload, which triggers ERS and excessive autophagy, ultimately leading to cardiac fibrosis (159). Ren *et al* (160) found that milk fat globule-egf factor 8 (MFG-E8) gene defects exacerbated pancreatic fibrosis. By contrast, pancreatic fibrosis was attenuated in cerulein-induced chronic pancreatitis mice treated with

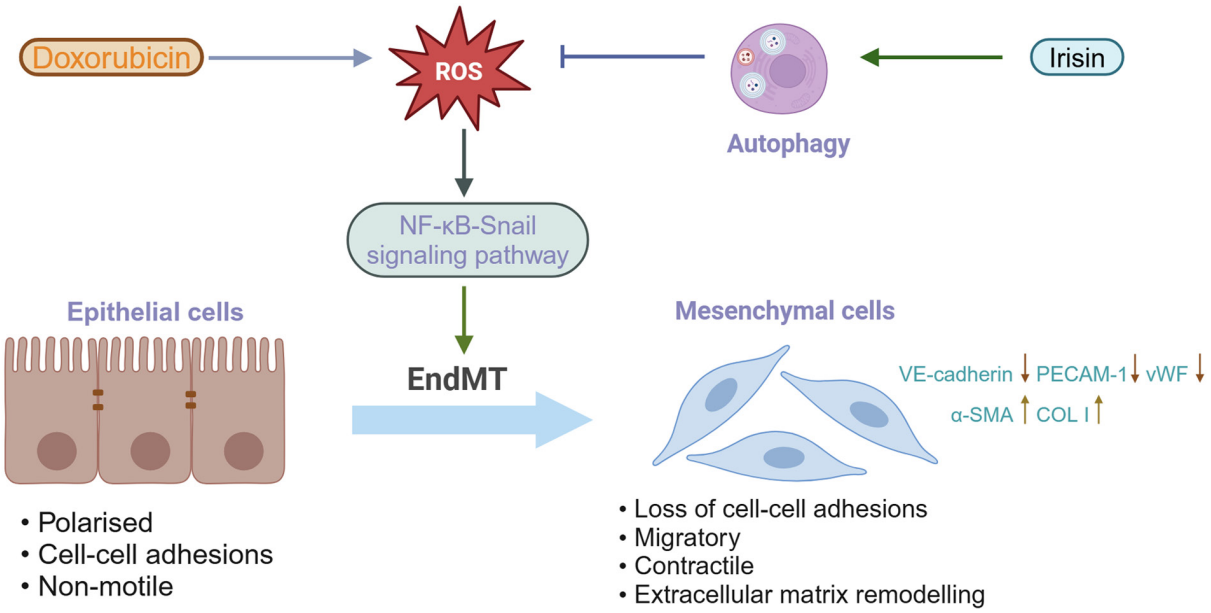

Figure 5. Autophagy-mediated endothelial-mesenchymal transition. Autophagy disorders lead to ROS accumulation, which can activate the NF-κB-Snail pathway, ultimately inducing EndMT. Irisin can improve autophagy disorders, eliminate ROS and reverse EndMT. During EndMT, the cellular morphology transitions from cobblestone-like to spindle-like. The capacity for antiplatelet generation is impaired and cell-to-cell connectivity and polarity is lost, whereas mesenchymal properties, such as invasion and migration, are enhanced. The expression of VE-cadherin, PECAM-1 and vWF is increased and the expression of α-SMA, waveform protein and type I collagen is decreased. COL I, collagen type I; PECAM1, platelet and endothelial cell adhesion molecule 1; ROS, reactive oxygen species; VE-cadherin, vascular endothelial cadherin; vWF, von Willebrand factor; α-SMA, alpha smooth muscle actin.

injections of exogenous MFG-E8. Meanwhile, ERS and CMA levels were reduced in cerulein-induced chronic pancreatitis mice after the administration of exogenous MFG-E8. Further experiments revealed that MFG-E8 inhibited the ERS-induced CMA pathway by targeting the specific CMA activator QX77, which reversed the effects of MFG-E8. This suggests that MFG-E8 inhibits pancreatic fibrosis by suppressing the ERS-induced CMA pathway. Recombinant MFG-E8 is likely to be developed as a novel medication for pancreatic fibrosis in chronic pancreatitis (160). Zheng *et al* (161) found that tunicamycin-induced ERS was associated with family with sequence similarity 172, member A (FAM172A)-mediated calcium flux. The autophagic process was observed in both normal fibrous tissue and epidural scar tissue cell lines after tunicamycin treatment. Further experimentation revealed that overexpression of FAM172A inhibited the autophagic process in normal fibrous tissue and epidural scar tissue. However, when the expression of FAM172A was inhibited, the autophagic process was increased in both cell lines. In a mouse model, FAM172A inhibited epidural fibrosis. Thus, ERS-associated calcium currents mediate the downregulation of FAM172A expression, which promotes autophagy in fibroblasts, a critical pathogenic factor in epidural fibrosis (161).

In summary, ERS-mediated autophagy exhibits a promoting effect on fibrosis development.

Autophagy-mediated EndMT and fibrosis. EndMT, a special type of epithelial-mesenchymal transition (EMT), refers to the process in which endothelial cells lose their original characteristics and transform into mesenchymal cells under the action of multiple stimuli. During the transformation process, endothelial cells gradually lose their morphology and function and acquire mesenchymal cell phenotypic characteristics such as proliferation, migration and collagen synthesis (162). In the process of acquiring the mesenchymal phenotype, endothelial cells (ECs) lose endothelial-specific markers such as vascular endothelial cadherin, platelet and endothelial cell adhesion molecule 1 and vonWillebrand factor. Instead, they start to express mesenchymal markers, such as vimentin, α-smooth muscle actin and type I collagen (163,164). At the same time, the cell morphology changes from compact cobblestone-like to elongated spindle-like. Cells acquire an impaired antiplatelet-generating capacity and loss of cell-to-cell connectivity and polarity, but enhanced mesenchymal cell properties, such as invasion and migration. Partial EndMT is a process in which ECs remain in an intermediate stage of transdifferentiation for an extended period rather than permanently acquiring a mesenchymal phenotype (165). This is the stage at which cells gain a mesenchymal phenotype, while retaining endothelial markers and exhibiting progenitor-like characteristics. This intermediate stage of phenotypic transformation is unstable and can be reversed under certain conditions, making it a potential target for therapy (166,167).

EndMT has been shown to promote the formation of heart valves and septa during embryonic development and has also been indicated to contribute to certain pathological conditions, such as cardiac and renal fibrosis and PF, tumor progression, and wound healing processes (168). ECs, however, are not fully understood regarding their regulatory role in cellular metabolism to drive EndMT. Currently, it has been found that autophagy regulates the EndMT, which contributes to the development of fibrotic diseases (Fig. 5). Zhang *et al* (169) showed that advanced glycosylation end-products (AGEs)/AGE receptor (RAGE) regulates autophagy in heart failure, which results in EndMT-induced cardiac fibrosis. RAGE knockdown inhibited autophagy-regulated EndMT, attenuated cardiac

fibrosis and improved cardiac function. Therefore, mechanistic studies focusing on the AGEs/RAGE-autophagy-EndMT axis may provide novel therapeutic targets for the treatment of heart failure (169). Pan *et al* (170) found that early perivascular fibrosis induced by doxorubicin was associated with the EndMT program. Disturbed autophagy leads to ROS accumulation, and ROS can trigger NF-κB-Snail activation, which could be the basis for doxorubicin involvement in EndMT induction. In an animal model of disseminated intravascular coagulation, irisin attenuated perivascular fibrosis and EndMT. Irisin can improve autophagy disorders, eliminate ROS and reverse EndMT by modulating uncoupling protein 2, irisin's proven target. ROS accumulation and autophagy disorders are identified as the factors contributing to EndMT in CMEC, which is involved in the initiation and development of perivascular fibrosis in disseminated intravascular coagulation (170) (Fig. 5). Zhou *et al* (171) analyzed the late proliferative endometrium of both normal patients and those with severe intrauterine adhesions (IUA), confirming that the endometrial tissue in patients with IUA exhibited autophagy deficiencies, which promoted EMT and fibrosis. Further analysis of the sequencing results of autophagy-related gene expression revealed that the most significant differential gene, iodothyronine deiodinase 2, triggers autophagy defects in endometrial epithelial cells through the MAPK/ERK-mTOR pathway, leading to EMT. Meanwhile, *in vivo* experiments also confirmed that targeting autophagy could inhibit EMT and alleviate fibrosis (171). Singh *et al* (172) found that the deletion of ATG7, an essential autophagy gene in ECs, resulted in disrupted autophagic flux, an increase in mesenchymal markers, loss of ECs and significant changes in the structure of the ECs. In *in vitro* experiments, deletion of ATG7 led to upregulation of key pro-fibrotic genes and TGF-β signaling. In *in vivo* experiments, mice with specific knockout of ATG7 in the ECs exhibited a reduction in endothelial-specific markers. Higher sensitivity to collagen accumulation and bleomycin-induced PF was also observed. The study provided novel evidence indicating that the loss of *in vivo* endothelial autophagy exacerbates the fibrotic response in mice. This occurs through a regulatory effect of autophagy to restrain TGF-β-dependent EndMT. These findings suggest that it is possible that autophagy regulates the crosstalk between EndMT and organ fibrosis. The autophagy gene ATG7 has been demonstrated to regulate organ fibrosis by modulating shifts in EndMT (172).

Other autophagy-related processes and fibrosis. Autophagy is able to change the secretory phenotype of tissue cells. For example, autophagy leads to a secretory phenotype that facilitates the production of profibrotic cytokines, which results in the secretion of the corresponding pro-fibrotic cytokines, leading to fibrotic disease progression. Livingston *et al* (173) found that autophagy was sustained at high levels in renal tubular cells after ischemic acute kidney injury, leading to the expression and secretion of fibroblast growth factor (FGF)2. FGF2 is a key paracrine factor produced by renal tubular cells of the secretory phenotype that promotes fibroblast activation and interstitial fibrosis during maladaptive renal repair (173). Zhou *et al* (154) demonstrated that ERS in fibroblasts triggers the upregulation of autophagy, which promotes the phenotypic transformation of fibroblasts and the synthesis and secretion of collagen. The study also found that autophagy regulates the secretion of inflammatory factors, which contribute to the development of fibrotic diseases. In a study by Nam *et al* (174), after unilateral ureteral obstruction, autophagy induced in distal renal tubular epithelial cells was demonstrated to confer protection against renal tubular interstitial fibrosis by modulating the TGF-β/SMAD4 signaling pathway and the NLRP3 inflammatory vesicle/caspase-1/IL-1β signaling pathway.

5. Conclusions and perspectives

There is a great deal of scientific evidence that the development of fibrotic diseases is profoundly influenced by autophagy. Autophagy can promote or inhibit fibrosis in organs and tissues in several mechanisms. Over the past years, numerous researchers have contributed to the discovery of autophagy's role in fibrosis as well as its potential as a therapeutic target. Significant breakthroughs have been made in the development of targeted antifibrotic medicines against autophagic mechanisms. Liu *et al* (175) found that, through regulation of the autophagy-lysosomal pathway and RAB27A, arrestin beta 1 enhances the release of MBL-associated serine protease 1 (MASP1)-enriched extracellular vesicles from hepatocytes. Their follow-up experiments revealed that activation of hepatic stellate cells through P38 MAPK/ATF2 signaling promotes liver fibrosis, with hepatocyte-derived MASP1 being a crucial factor. Therefore, MASP1 may have high potential to be developed as a critical therapeutic target for liver fibrosis (175). Wang *et al* (11) found that lycopene slows aristolochic acid 1-induced renal fibrosis by activating mitochondrial autophagy and inhibiting renal cell EMT. Therefore, the targeted modulation of mitochondrial autophagy represents a promising new approach to treat chronic kidney disease. Lycopene is promising as a novel medicine with unexpected effects for treating renal fibrosis (11). Also, according to Li *et al* (176), excessive apoptosis and insufficient autophagy in AMs coexisted during the evolution of idiopathic pulmonary fibrosis (IPF). Zukamu, a traditional Chinese medicine, regulates the 'autophagy-apoptosis' balance in AMs, thus inhibiting the fibrosis process to a certain extent. This demonstrated that it may be possible to treat IPF by inhibiting apoptosis of AMs and promoting the autophagic activity of AMs, which is another novel perspective for treating fibrotic diseases and provides valuable insights for future mechanistic studies and targeted new medicine development (176). Therefore, the treatment of fibrosis by promoting or inhibiting autophagy has great potential for the future.

The exploration of the relationship between autophagy and fibrosis provides an important reference for academic research and clinical practice. i) Elucidation of disease mechanisms: In-depth study of the mechanism of autophagy in fibrosis contributes to a comprehensive understanding of the pathological process of the disease (11,177). ii) Guiding future research directions: The present review provides new perspectives on research in autophagy, facilitating interdisciplinary collaboration and advancing medical development (178). iii) Potential therapeutic targets: The development of medicines targeting autophagy-related molecules offers a novel direction for fibrosis treatment (11,175). iv) Disease course prediction: The

alteration of autophagy-related protein expression levels in fibrotic tissues may serve as a biomarker for disease progression and treatment efficacy (87-95). This serves as a crucial reference for early diagnosis, prognosis assessment and individualized treatment planning in the clinic. Clarifying various autophagy regulatory pathways would facilitate the identification of particular autophagy regulatory mechanisms in distinct organs during fibrosis, hence advancing precision medicine and improving therapeutic efficacy.

However, the relationship between autophagy and fibrosis remains largely unexplored. Although there are various types of autophagy, current research on autophagy and fibrosis predominantly focuses on macroautophagy and the role of other types of autophagy, such as CMA, various selective autophagies and microautophagy, in fibrosis remains to be elucidated. Further, the interactions between autophagy and other physiological or pathological responses, such as ferroptosis, pyroptosis, apoptosis and inflammatory responses, require thorough examination. This will contribute to a more comprehensive, integrated and in-depth understanding of the function of autophagy in cellular physiological and pathological responses. In addition, the assessment of autophagic activity is mainly based on the amount of LC3-II detected, but it does not provide any accurate feedback on the dynamic autophagic process. In addition, suitable monitoring indicators are required to accurately reflect autophagic flux or autophagic degradation. Finally, from a clinical perspective, there is a necessity for more efficacious and targeted autophagy-targeting medicines. While the majority of the current evidence of the role of autophagy in fibrosis was obtained from animal models and *in vitro* cultured cells, it is still unknown whether these findings derived from *in vitro* cells and animals can be translated to humans. A method to monitor human autophagic activity is required to assess the effect of autophagy on human fibrotic diseases and the therapeutic progress. Although significant advancements have been achieved in understanding the effect of autophagy on fibrosis, it is essential to address these challenges so that existing and forthcoming new strategies can be better utilized to modulate autophagy for the benefit of patients with fibrotic diseases.

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Authors' contributions

YC was primarily responsible for the writing, review and revision of the article. ZW participated in the literature review and provided feedback for this review. QM and CS provided guidance throughout the preparation of this manuscript and made significant revisions to the text. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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