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Mitophagy in tumours: friend or foe?

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Abstract

Mitophagy is a specific type of autophagy and a selective form of autophagy on a larger scale. It selectively eliminates damaged, misfolded, and surplus mitochondria, particularly those that are cytotoxic, by using autophagic lysosomes. This process is crucial for maintaining a balance of both the quality and quantity of mitochondria, which is necessary for normal cell function and tissue development. However, in certain abnormal situations, such as nutritional deficiencies and hypoxia, the function of mitophagy becomes impaired. This leads to a failure to clear damaged mitochondria in a timely manner, resulting in the production of a large number of reactive oxygen species. These reactive oxygen species further contribute to an inflammatory response and the release of factors that induce apoptosis. Moreover, abnormal mitophagy can also cause mitochondrial dysfunction, disrupt metabolic reprogramming during stress responses, alter cell fate decisions and differentiation, and consequently impact the development and progression of diseases, including cancer. Therefore, mitophagy plays a crucial role in controlling the quality of cancer cells, making it imperative to study its function and impact. Numerous proteins and molecules are involved in the regulation of mitophagy, with Parkin and PTEN-induced kinase 1 (PINK1) serving as key mediators, and the hypoxia-related proteins hypoxia-inducible factor la (HIF1a) and FUN14 domain-containing 1 (FUNDC1) also playing a role. Additionally, proteins such as chromatin licensing and DNA replication factor 1 (CDT-1), insulin-like growth factor 1 (IGF-1), caveolin 1 (Cav-1), and others contribute to the regulation of mitophagy in various ways. This article aims to explore the dual role of mitophagy in tumourigenesis by examining the factors and proteins associated with mitophagy and their regulatory effects. The objective of this review is to provide a new theoretical foundation and direction for cancer treatment. **(Endokrynol Pol 2023; 74 (5): 511–519)**

Key words: *mitophagy; tumour; treatment*

Introduction

Mitochondria are the main sites of aerobic respiration of eukaryotic cells and the energy power stations of cells, and they are involved in indispensable functions of the cell, including adenosine triphosphate (ATP) production, calcium ions (Ca^{2+}) regulation, reactive oxygen species (ROS) production and scavenging, regulation of apoptotic cell death, etc. Mitochondrial dysfunction is largely involved in aging, cancer, age-related neurodegeneration, and metabolic syndrome [1, 2]. Autophagy is an intracellular catabolic process of delivering cytosol and/or its specific content to the lysosomes for degradation [3]. Mitophagy is a special form of autophagy; autophagy lysosomes selectively remove damaged, folded, and redundant mitochondria, especially for damaged cytotoxic mitochondria, to maintain the balance of mitochondrial quality and quantity, which is essential for normal cellular physiology and tissue development [4]. When mitochondria are stimulated by stresses such as nutritional deficiencies, hypoxia, DNA damage, inflammation, and mitochondrial membrane depolarization, mitophagy is activated, and damaged mitochondria can be selectively cleared by cells through the mitophagy pathway, thereby maintaining the structural and functional integrity of mitochondria [5]. However, when the mitophagy function is abnormal, the damaged mitochondria cannot be cleared in time, and they generate a large amount of ROS. On the one hand, the ROS damage normal mitochondria and promote the inflammatory response; on the other hand, it can release apoptosis factors and induce apoptosis [6, 7]. Abnormal mitophagy can also cause mitochondrial dysfunction, which affects metabolic reprogramming in response to stress, changes the determination and differentiation of cell fate, and thus affects the occurrence and aetiology of diseases, including cancer [8] (Fig. 1).

In recent years, the regulatory mechanism of mitophagy and its impact on human physiology and pathology has been the focus of many researchers. Dissection of the functions of some of the regulators and molecular adaptors involved in targeting mitochondria to the autophagosome has increased our understanding of how mitophagy is initiated and executed. The most widely used among these mitophagy regulators are Parkin and PTEN-induced kinase 1 (PINK1), as well

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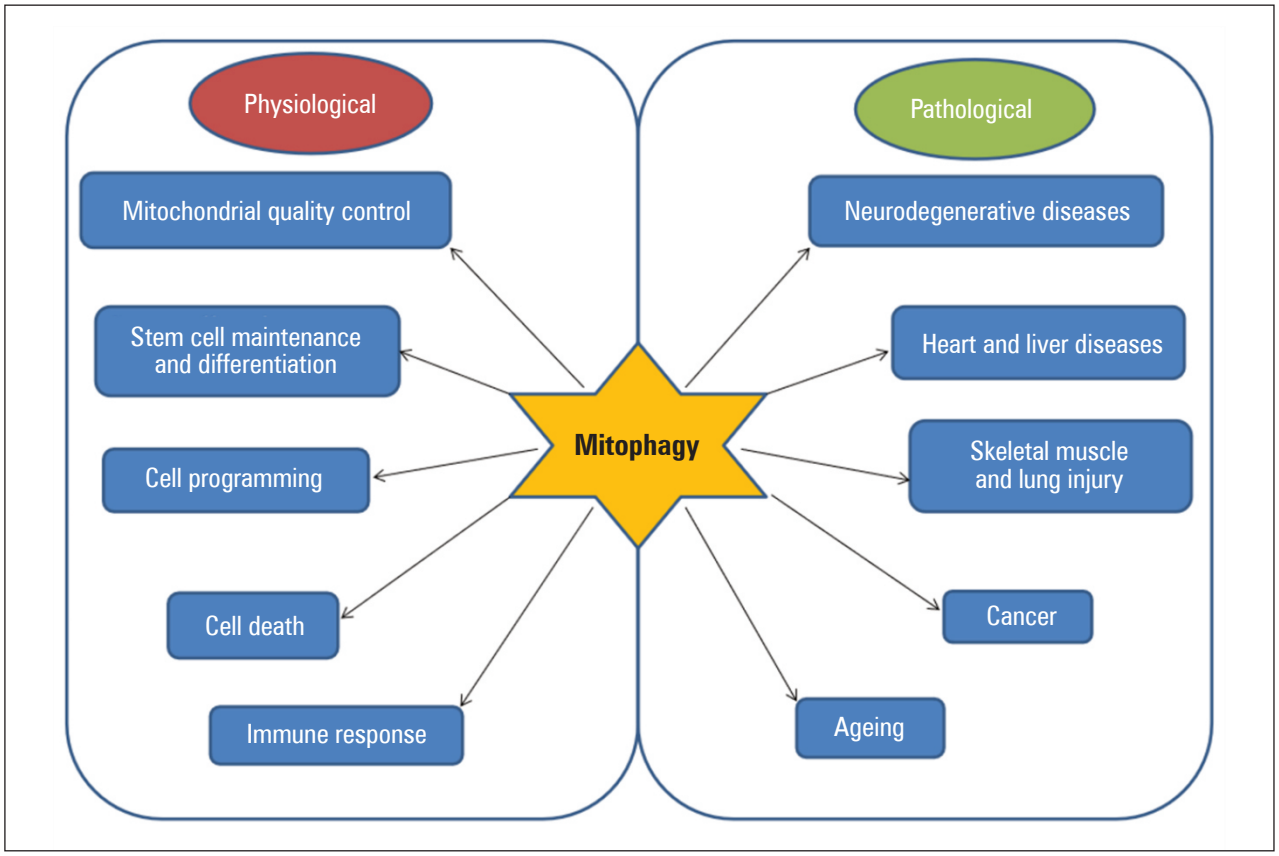

Figure 1. *The role of mitophagy in normal physiology and human disease. Mitophagy plays an important role in maintaining mitochondria homeostasis and various aspects of cellular function*

as BCL-2 adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) and BNIP3-like (BNIP3/NIX), which plays a unique and non-overlapping role in promoting mitophagy. Other participants [such as multifunctional E3 ubiquitin ligase (Mul1) and FUN14 domain-containing 1 (FUNDC1)] are emerging and may become the focus of future research [9–11] (Fig. 2). Also, drugs can affect mitophagy by interfering with autophagosome formation, hypoxia-inducible factor (HIF) activation, autophagosome and lysosome fusion, and ubiquitination under hypoxia conditions [12].

Cancer is a worldwide problem. How to prevent and treat cancer has always been the focus and difficulty of research. The impact of mitophagy on tumours has both beneficial and harmful aspects. Regulating mitophagy to inhibit the occurrence and development of tumours can provide new targets for tumour treatment in the clinic.

Mitophagy is the enemy of tumours: mitophagy can inhibit tumour development

Increasing evidence indicates that defects in the mitophagy machinery may play a role in the progression of cancer [13]. Parkin (PARK2) and PINK1 (PARK6) are key mediators of mitophagy; PINK1 is a kinase localized to mitochondria, whereas Parkin is an E3 ubiquitin ligase located in the cytosol [14, 15]. Mutations of PINK1 and Parkin are often detected in a variety of tumours, including lung cancer [16], ovarian cancer [17], glioblastoma/glioma [18], colorectal cancer [19], and breast cancer [20] (Tab. 1). It has been found that the PARK2 gene is significantly associated with adenomatous polyposis in human colorectal cancer, and PARK2 overexpression can inhibit the proliferation of colon cancer cells [19]. Also, after crossing PARK2 gene knockout mice with colorectal adenomatous polyposis, the development of intestinal adenomas in newborn mice was rapidly accelerated and polyp diversity increased, indicating that PARK2 is a tumour suppressor gene [13]. Another cancer often observed with abnormal Parkin is glioblastoma multiforme. Using data from the cancer genome atlas, it was found that about a quarter of glioblastoma multiforme specimens have PARK2 heterozygous or homozygous deletions [18]. In addition, in the absence of somatic mutations in PARK2, p53-mediated loss of Parkin transcription is considered to be a factor that promotes glioma development [21]. Neuroblastoma is a solid extracranial tumour that occurs in the sympathetic nervous system. Recently, mutations in mi-

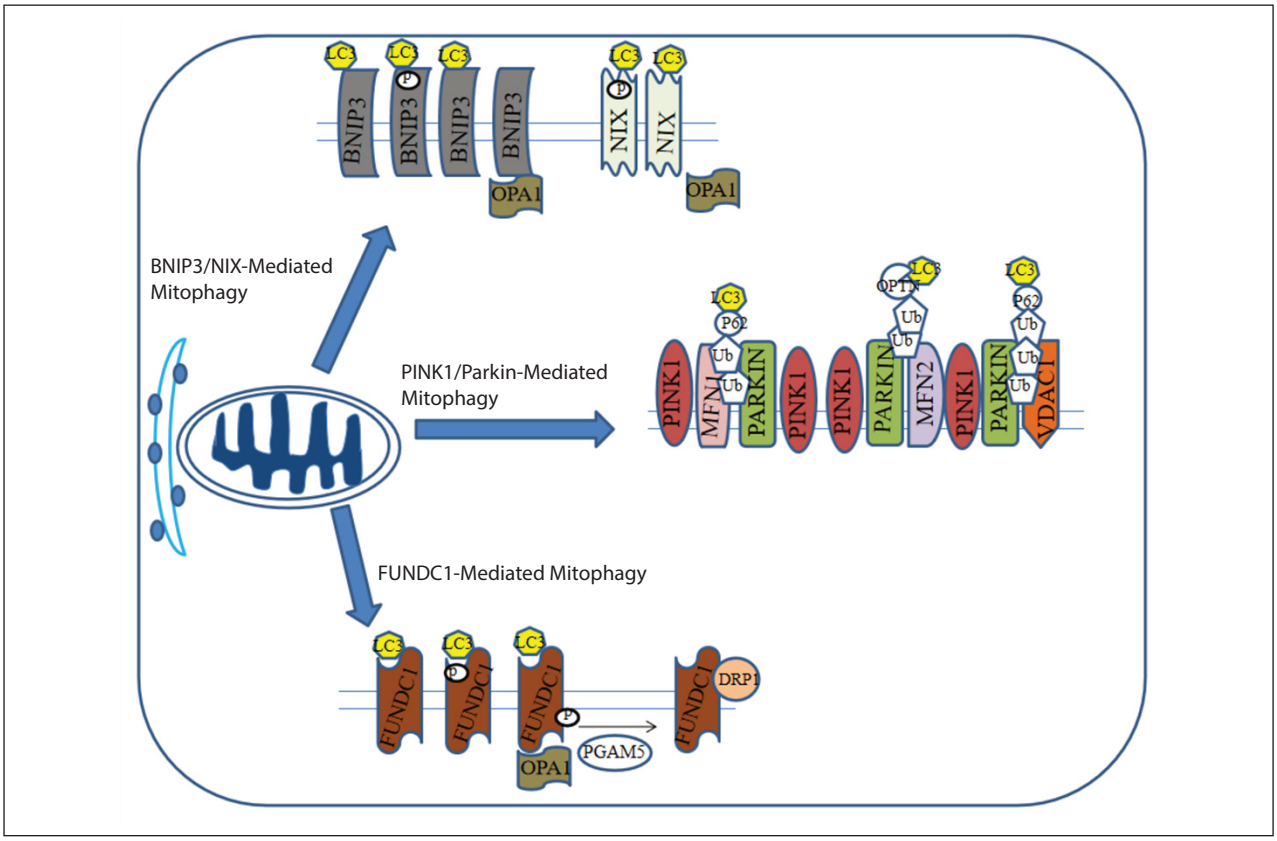

Figure 2. *The main mechanisms and related proteins of the typical mitophagy pathway are summarized. PTEN-induced kinase 1 (PINK1)/Parkin-mediated ubiquitination of mitochondrial proteins connects the autophagy cargo receptor sequestosome 1 (p62/SQSTM1) and optineurin (OPTN) to mitochondrial/autophagosome interactions. In addition, BCL-2 adenovirus E1B 19 kDa-interacting protein 3 (BNIP3), NIX, and FUN14 domain-containing 1 (FUNDC1) can directly bind to light chain 3 (LC3) molecules that modify autophagosomes, and the mechanism is regulated by their phosphorylation status*

tophagy were found in patients with neuroblastoma, including in PARK6 [18]. A subtype of neuroblastoma known to have a poor prognosis is characterized by the oncogene MYCN amplification. Neuroblastoma cell line N-Myc and Parkin protein levels are negatively correlated [22]. Like glioblastoma, Parkin deletion is a common mutation in lung cancer. Due to autophagy inhibition, the upregulation of cyclin E138 and the accumulation of ROS are considered to be the drivers of lung cancer tumour progression [23]. The absence of mitophagy also affects the progression of breast cancer. The PARK2-containing FRA6E fragile region is commonly lost in some breast cancers, and changes in PARK2 copy numbers are relatively frequent in aggressive triple-negative tumours, supporting the role of Parkin as a tumour suppressor [20]. Mitophagy also plays a role in breast cancer by affecting adjacent stromal cells to alter the tumour microenvironment. Therefore, the ablation of PINK1/Parkin-mediated mitophagy and alternative forms of mitophagy can promote the progression of breast cancer [24]. Moreover, according to Biel and Rao, breast cancer cells use mitophagy to exert therapy resistance [25]. Biel and Rao highlight that anti-mitophagy molecules such as the mitochondrial translocator protein (TSPO) are overexpressed in aggressive forms of cancer. However, mitophagy is induced just in the aggressive breast cancer cell line MDA-MB-231 and not in the primary mammary epithelial cells (MCF-12A) [25]. Sublethal concentrations of TPP-conjugated redox molecules, including mitoapocynin (MitoA) and mitoquinone (MitoQ), exploit the increased Δ m reported in aggressive cancer cells leading to continued mitophagy [25]. Ovarian cancer shares some key features with neuroblastoma and breast cancer. N-Myc and cyclin E are both upregulated in these tumour subpopulations [26, 27]. N-Myc proved to be a transcription inhibitor of Parkin1, while cyclin E accumulated when Parkin was deleted [16, 22]. It is interesting to speculate that Parkin may indirectly act as a potential cell cycle regulator in ovarian cancer.

The hypoxic environment provides a good microenvironment for cancer stem cells, increasing the possibility of cancer progression and metastasis. Hypoxia will activate hypoxia-inducible factor la (HIF1a). HIF1a is the main transcription and regulatory factor for cell adaptation to hypoxia, which can regulate the expression

Table.1 Relationship ***between mitophagy regulators and tumour***

Protein	Trait and function	Links to cancer/disease	Reference
Parkin	Parkin is recruited by PINK1 and is phosphorylated at serine 65 of its ubiquitin-like domain. It is an E3 ubiquitin ligase from the RBR domain-containing family. It discharges ubiquitin from an E2 onto a catalytic cysteine, producing a thioester intermediate, before conjugating the ubiquitin onto a substrate	PARK2 inactivation is associated with Parkinson's disease. It is absent in human ovarian, breast, lung, and bladder cancers. Inactivated mutations are found in glioblastomas and other cancers. No Parkin mice developed spontaneous liver tumours and were sensitive to radiation-induced lymphoma. In addition, Parkin was poorly expressed in melanoma, oropharyngeal squamous cell carcinoma, pancreatic cancer, adenoid cystic carcinoma, ampulla carcinoma, and colorectal cancer.	[17, 19, 20, 67–70]
PINK1	PINK1 is a mitochondrial serine/threonine protein kinase that contains an N-terminal MTS. Under normal conditions, due to its N-terminal MTS, PINK1 is constitutively imported into the mitochondria via the TOM and TIM complex	PARK6 deletion is associated with Parkinson's disease. Reduced expression of PARK6 has been detected in glioblastoma and ovarian cancer, and mutations in PARK6 have been detected in neuroblastoma.	[8, 71–73]
BNIP3	BNIP3 is one of 3 proteins identified in the screening for adenovirus E1B-19 K-interacting proteins, which exhibited pro-death activity. BNIP3 and BNIP3L (also known as NIX) are hypoxia-inducible, tail-anchored proteins that integrate into the OMM via a carboxy terminal transmembrane domain	BNIP3 is absent, silent, or incorrectly located in breast, prostate, colon, pancreas, liver, lung cancer, glioma, and other cancers. It accelerated the metastasis of breast cancer in a mouse model.	[29, 30, 32, 74]
NIX	NIX also known as BNIP3L, induced by hypoxia and p53, required for mitophagy during red blood cell differentiation, interacts with LC3 and Rheb	NIX promotes tumour growth in mouse breast tumour xenograft studies and plays a role in heart disease.	[75–77]
FUNDC1	FUNDC1 is another mitophagy adaptor that functions at the OMM and interacts with processed LC3 through a conserved LIR. It is critical for hypoxia-induced mitophagy	FUNDC1 is highly expressed in cervical cancer, hepatocellular carcinoma, and laryngeal cancer.	[72, 78, 79]
NRF2	NRF2 is the master regulator of many cell protection genes. After translation, it will be rapidly degraded by the ubiquitin proteasome system in the cytoplasm	NRF2 plays a dual role in cancer. It regulates chemical and genetic lung cancer models.	[80–83]
IGF	IGF plays a vital role in cell growth, differentiation, and survival. It mainly activates the IGF-1R on the cell surface. The activation of IGF-1R stimulates multiple pathways and ultimately produces multiple biological effects in multiple tissues and cells	IGF-1R is overexpressed in a variety of malignant tumours, including lung cancer, breast cancer, prostate cancer, glioma, gastrointestinal cancer, and so on.	[46, 47, 84]
CK2	CK2 is a kinase phosphorylated by Atg32. It is a ubiquitous and highly conserved serine/threonine kinase that plays a central role in the control of multiple pathways of cell proliferation, transformation, apoptosis, and aging	CK2 is highly expressed in solid and blood-related tumours, such as breast cancer and lymphoma.	[56, 57, 85]
Src	Src kinase is abundant. FCCP and hypoxia can both inactivate Src kinase and CK2, and activate PGAM5 to promote FUNDC1 mediated mitophagy in mammalian cells	Src is found to be highly expressed in many human tumours, including lung, breast, pancreatic, colon, and prostate cancers.	[54, 85–87]
Cav-1	Cav-1 is a constituent protein of caveolae. It interacts with many signal molecules through the caveolin scaffold domain and participates in various physiological and pathological processes such as cell growth, regulation of mitochondrial antioxidant levels, apoptosis, and carcinogenesis	Cav-1 was found upregulated in multidrug-resistant colon cancer cells, Adriamycin-resistant breast cancer cells, and Taxol-and gemcitabine-resistant lung cancer cells.	[58, 88, 89]
BRCA1	BRCA1 plays an integral role in response to cellular stress via the activation of DNA repair processes	Germline mutations in the BRCA gene make individuals susceptible to breast and ovarian cancer, and increase the risk of pancreatic and prostate cancer.	[64, 90, 91]

FUNDC1 — FUN14 domain-containing 1; PINK1 — PTEN-induced kinase; IGF — insulin-like growth factor; CK2 — casein kinase 2; BNIP3 — BCL-2 adenovirus E1B 19 kDa-interacting protein 3; NIX — BCL-2 adenovirus E1B 19 kDa-interacting protein 3 like; NRF2 — nuclear factor erythroid 2-related factor 2; Cav-1 — caveolin 1; BRCA1 — breast cancer type 1 susceptibility protein; Src — proto-oncogene tyrosine-protein kinase

of apoptosis related proteins BCL-2 and BNIP3. BNIP3 is a pro-apoptotic BH3-only protein associated with the pathogenesis of many diseases, including cancer and cardiovascular disease, it can enhance mitophagy by inhibiting damaged mitochondrial fusion and making damaged mitochondria easier to eliminate [29]. For

example, in malignant glioma cells, BNIP3 expression is increased under the induction of ceramide, which further activates mitophagy and leads to cancer cell death [30]. Similarly, ethyl 3,4-dihydroxybenzoate activates mitophagy due to the high expression of BNIP3 when acting on oesophageal cancer cells, eventually leading to cancer cell death [31]. In a breast cancer aggressive mouse model, BNIP3 was also shown to inhibit tumour progression. In some cases, like Parkin loss, the loss of BNIP3 promotes tumour growth and metastasis by turning cells to tumourigenic glycolysis and increasing ROS production [32]. Mitochondrial outer-membrane protein, FUNDC1, is a mitophagy receptor that clears dysfunctional mitochondria in response to hypoxia and mitochondrial stresses; under hypoxic conditions, protein phosphatase 5 dephosphorylates FUNDCl, promoting advance FUNDCl to interact with microtubule-associated protein 1 light chain 3 (LC3) to promote mitophagy [33, 34]. Wenhui Li et al. found that the role of FUNDC1-mediated mitophagy in hepatocarcinogenesis (HCG) inhibited tumour initiation. In hepatocytes, due to the excessive activation of inflammatory bodies, the loss of FUNDC1 increases the susceptibility to HCG. However, in the later stages of tumour development, increased FUNDC1 expression is beneficial to tumour growth [35].

Divalent cation transporter 1 (DCT-1) is a transcription factor, a nematode homologue of nuclear factor erythroid 2-like 2 (NFE2L2); its expression is upregulated under mitophagy, and mediated by skinhead-1 (SKN-1), it is activated during oxidative stress to maintain mitochondrial homeostasis [36]. As a new regulatory factor of mitophagy, SKN-1 can stimulate the expression of core mitochondrial components and promote the assembly of new mitochondria and mitophagy regeneration [37]. It is worth noting that another mitophagy regulator, nuclear factor erythroid 2-related factor 2 (NRF2), is the main regulator of cellular redox homeostasis [38]. In recent years, it has been found that NRF2, as a part of cell protection gene expression regulator, affects mitochondrial function [39]. Studies using isolated mitochondria and cultured cells have shown that NRF2 deficiency can lead to impaired mitochondrial fatty acid oxidation, respiration, and ATP production. The small molecule activator of NRF2 supports mitochondrial integrity by promoting mitophagy and giving antioxidant stress-mediated osmotic transition [40]. The combined action of the above factors can also counteract the Warburg effect (the Warburg effect, also known as aerobic glycolysis, is defined as the propensity of cancer cells to take up high levels of glucose and to secrete lactate in the presence of oxygen) to increase the stability of mitophagy and autophagy, thereby protecting mitochondrial metabolism from carcinogenic transformation [41]. In addition, the protective effect of NRF2 activation in preventing chemical and radiation-induced carcinogenesis has been fully affirmed [42, 43]. NRF2 can ensure the rapid enzymatic modification and excretion of chemical carcinogens, and through the expression of its target genes to quench ROS or repair oxidative damage to prevent cancer, this anti-cancer effect of NRF2 has been extensively reviewed elsewhere [44, 45].

Another major protein that mediates mitophagy and tumour is insulin/insulin-like growth factor (IGF). IGF-1 signalling through phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin complex 1 (PI3K/AKT/mTORC1) signalling pathway has a wide range of effects in cell growth, oncogenic transformation, and cancer progression [46]. In addition, IGF-1/PI3K signalling can stimulate mitochondrial biogenesis and mitophagy [47], mainly through the induction of peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1) transcription activator and PGC-1 related coactivator (PRC), and the induction of mitophagy important mediator BNIP3 [32]. In this way, IGF-1 signal transduction enables cells to maintain a healthy mitochondrial pool to promote cell bioenergy efficiency and mitochondrial homeostasis. Amy Lyons et al. suggested that IGF-1-mediated mitochondrial protection plays a major role in metabolic reprogramming and resistance to targeted cancer treatments [48]. The continuously increasing IGF-1 receptor (IGF-1R) signal maintains the healthy growth of mitochondria while eliminating dysfunctional mitochondria, to prevent the accumulation of ROS, thereby improving the ability of cells to resist stress [48]. Specific targeting of insulin and IGF receptors in cancer cells is a potentially effective strategy for anti-cancer therapy. Because mitophagy confers some beneficial regulatory effects on low insulin signal transduction, increased insulin/IGF signal transduction can induce specific types of tumour mitophagy in mitochondria, thereby inhibiting tumour progression.

Mitophagy is the friend of tumours: mitophagy can promote tumour development

The beneficial effects of mitophagy are discussed in many pathological processes, including high-fat diet-mediated fatty liver, myocardial hypoxia-reoxygenation injury, oxidative stress-induced endothelial dysfunction, and acute kidney injury [49, 50]. The protective effect of mitophagy is mainly achieved by clearing ROS, reversing calcium balance, staining mitochondrial membrane permeability, and inhibiting mitochondria-dependent cancer death [51]. Tylichova et al. found that the use of short-chain

and N-3 polyunsaturated fatty acids on human colon cancer HT29 and HCT116 cells could induce mitophagy, which had a protective effect on colon cancer cells and prevented them from being affected by drugs [52]. Mitophagy can avoid the differentiation of cancer cells induced by sodium butyrate and programmed death of cancer cells, and the damaged mitochondria can be digested, decomposed, and reused, and the mitophagy pathway can be used to promote the survival of tumour cells [52]. Studies have also found that hypoxia can promote autophagy by regulating the translation level of HCT116 in colon cancer cells. In this process, lysosomal glycoprotein prosaposin (PSAP) and lysosome-associated membrane protein-2 (LAMP2), which are highly conserved, induce mitophagy by upregulating the translation level, thus protecting tumour cells [53]. In addition, 12 kinds of mitochondrial-specific glycoproteins (MRPL36, MRPL12, MRP63, MRPL41, MRPS7, MRPS34, MRPS16, MRPL43, MRPL34, MRPS12, MRPL38, and MRPS26) can also promote mitophagy by up-regulating the translation level of colon cancer cells, which in turn is beneficial to the survival of HCT116 colon cancer cells [53].

Other factors that regulate hypoxia-induced mitophagy also play an important role in cancer cell homeostasis and tumour progression. The most common ones are Src and casein kinase 2 (CK2). Src family kinases (SFK) play a key role in cell adhesion, invasion, proliferation, survival, and angiogenesis during tumour development [54]. Overexpression or high activation of SFKs often occurs in tumour tissues, and they are the central mediators of many important signal pathways in tumourigenesis. SFK can affect cell proliferation through the Ras/ERK/MAPK pathway and can regulate gene expression through transcription factors such as STAT molecules [55]. CK2 is a serine/threonine-protein kinase that is highly conserved among eukaryotes and plays roles in many different cellular processes, such as cell survival, cell polarity, cell cycle regulation, stress responses, transcription and translation, and regulation of mitophagy by directly phosphorylating Atg32 [56]. The increased expression of CK2 in mice leads to the occurrence of various types of cancer (including solid and blood-related tumours, such as breast cancer, lymphoma, etc.), revealing its carcinogenic properties [57]. CK2 is in many key tumour-related organisms; it plays an important role in the process of learning, including cell apoptosis, DNA damage response, and cell cycle regulation. CK2 has become a potential anti-cancer target [57]. Different CK2 inhibitors have been developed for various cancers with anti-tumour properties.

Studies have shown that caveolin 1 (Cav-1) is a powerful biomarker of tumour progression and metastasis in the cell matrix. ROS released by cancer cells can induce the loss of Cav-1 in the matrix and further induce the metabolic changes of the tumour cell-matrix, leading to mitochondrial dysfunction and further enhancing mitophagy [58]. The loss of stromal Cav-1 not only predicts early tumour recurrence, lymph node metastasis, and poor survival rate, but also predicts the progression of ductal carcinoma *in situ* in patients to aggressive disease, suggesting that the loss of interstitial Cav-1 can regulate tumour progression [59]. There is a novel idea called the "autophagic tumour stroma model of cancer", i.e. the loss of stromal cells Cav-1-induced autophagy/mitophagy in tumour stroma through oxidative stress; this creates a catabolic micro-environment in which the local accumulation of chemicals and circulating nutrients (such as amino acids and nucleotides) directly supplies cancer cells for survival and growth [60]. In addition, Cav-1 can negatively regulate transforming growth factor β (TGF-β), and the activation of TGF-β signalling is important for inducing mitophagy in tumour stromal cells [61]. In fact, in tumour stromal cells, the activation of TGF-β signalling that depends on paracrine or autocrine can induce abnormal metabolism of the tumour microenvironment, leading to oxidative stress, increased autophagy/mitophagy and glycolysis, and down-regulation of Cav-1. These metabolic changes can spread between neighbouring fibroblasts to maintain tumour cell growth [62, 63].

Breast cancer type 1 susceptibility protein (BRCA1) is a well-recognized tumour suppressor gene [64]. However, BRCA1-deficient ovarian cancer cells influence the metabolism of fibroblasts in the surrounding stroma by producing high levels of hydrogen peroxide, which activates nuclear factor-kappa B (NF-κB) signal transduction to induce mitophagy in tumour stroma cells, thereby promoting tumour growth [65]. Some cytokines or other bioactive factors, such as migration stimulating factor (MSF), as a genetically truncated N-terminal isoform of fibronectin that is highly expressed during mammalian development in foetal fibroblasts, and during tumour formation in human cancer-associated myofibroblasts, can activate the TGF-β and CD42-NF-κB in tumour stromal cells induced by mitophagy and promote tumour cell growth [66].

In general, mitophagy is activated by oncogenic signal transduction pathways, including the TGF-$\beta$and NF-κB pathways, which regulate cancer cell metabolism to promote tumour cell growth. Therefore, further inhibition of mitophagy in tumour stroma may be a feasible strategy to inhibit tumour cell growth by neutralizing ROS or inhibiting metabolic uncoupling to inhibit TGF-β and NF-κB signal transduction levels in tumour cells and their surrounding stromal microenvironment. This provides useful hints for targeting mitophagy and a potential anticancer strategy.

Conclusions

Mitophagy is becoming a link between cells and physiology. Transcription factors related to mitophagy can also affect the development process of tumours, and the degree of mitophagy is crucial for the occurrence and development of tumours. Damage of mitophagy in healthy tissues can promote the formation and development of tumour cells, while mitophagy in hypoxic tumours can induce the survival of tumour cells. How to fully understand and utilize the regulatory mechanism of mitophagy to inhibit the development of tumours and avoid its beneficial side to tumours can be regarded as a research direction for the treatment of tumours.

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Ethics approval
Not applicable

Competing interests
Not applicable.

Authors' contributions
F.H. contributed to all aspects of this study and article. L.L. contributed to the study conception, design, data analysis and interpretation, and the critical revision of the article. All authors read and approved the final version of the manuscript.

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Disclosure statement
The authors declare that they have no potential conflicts of interest related to this work.

Availability of data and materials
All data used and/or analysed during the present study are available from the corresponding author on reasonable request.

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