Review Article

Mitophagy and oral cancers

ABSTRACT

Mitophagy is a progressive process that selectively targets weakened, old and damaged mitochondria, by an autophagic pathway, causing its destruction. Mitophagy maintains normal cellular physiology and tissue development, thereby controlling the cohesiveness of the mitochondrial pool. The mechanisms of mitophagy, tumorogenesis, and cell death are usually interrelated with each other and could be initiated by definite stressful conditions like hypoxia and nutrient starvation, which leads to the overall reduction in mitochondrial mass. This impedes the production of reactive oxygen species, and conserves nutrition, leading to cell survival in such extreme conditions. The inability to harmonize and regulate mitochondrial outcome in response to oncogenic stress can either stimulate or suppress tumorogenesis. Therefore, the relationship between mitophagy, tumorogenesis, and cell death plays an important role in the identification of potential targets of cell death and selective wiping out of cancer cells. This review portrays the mechanism of mitophagy, along with its role in cancers especially on oral cancers, and its importance in cancer therapeutics.

Keywords: Autophagy, cell death, mitophagy, oral cancers, treatment, tumorogenesis

INTRODUCTION

Autophagy (Atg) is a catabolic self-degenerative intercellular mechanism, associated with the recycling of damaged and dysfunctional cell organelles, proteins, and pathogens by the formation of a phagophore; that matures and expands to form autophagosomes which is degraded by lysosomes.[1,2] Atg plays an important role in eliminating toxic products from the cell and recycles amino acids, nucleic acids, fatty acids, and adenosine triphosphate (ATP) by lysosomes and aids in cellular survival in extremely stressful conditions. There are several degenerative types of Atg, that are totally nonselective for cytoplasmic elements whereas others, selectively target cytoplasmic elements and is usually referred to as targeted Atg.[3-5]

Mitophagy is a type of targeted Atg that involves selective degradation of mitochondria. Several studies conducted in recent years suggest two major mitophagy pathways that are centered on PINK1/Parkin and BNIP3/NIX by which degraded mitochondria combine with a phagophore to form autophagosome, and is usually regulated by proteins of the LC3 (microtubule-associated protein light chain 3) family.[3,6-8]

Mitochondria play an important role in normal cellular and tissue development and also aids in energy production by the formation of ATPs. It also regulates Ca^2+ hemostasis and regulates the production of reactive oxygen and nitrogen species (RONS), as also is the prime cell organelle involved in initiating several forms of cell death. Dysfunctional mitochondria display a potent danger as inadequate supply of ATP or excessive production of RONS can result in several disorders including cancers [Figure 1]. Therefore, the removal of damaged mitochondria is necessary for maintaining normal cellular integrity and tissue development.[6,7]

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REGULATION OF MITOPHAGY

Atg usually describes lysosomal-mediated degradation of intracellular contents, which can be divided into three basic mechanisms: (a) chaperone-mediated Atg, (b) micro-Atg, and (c) macro-Atg. Macro-Atg is the most extensively studied Atg, which involves the formation of double-membrane structures that encircle proteins, lipids, and organelles.[9] Degradation of mitochondria through the macro-Atg pathway is termed mitophagy.[10]

The term "mitophagy" was coined by Lemasters in 2005 to describe the selective Atg in yeast and emphasized the nonrandom nature of the process in yeast after the identification of SUN family protein UTH1.[11] Although Atg proteins involved in mitophagy has been identified clearly in yeast, namely Atg 32, similar Atg proteins if they exist in mammals is yet to be identified. However, NIX/BNIP3 L (NIP3-like protein X), BNIP3, FUNDC1 (FUN14 domain containing 1) and Cardiolipin function as receptors for LC3, which includes LC3A, LC3B, LC3B2, LC3C proteins, and belongs to the Atg8 family.[7] Another mechanism utilizes the presence of mitochondrial proteins followed by interaction with the adaptor proteins to interact with LC3, viz. the PINK1-Parkin (Parkinson juvenile disease protein 2) pathway where p62 and Nbr1 act as adaptor proteins.[12]

PATHWAYS OF MITOPHAGY

PINK1-Parkin

Pink1 and Parkin-mediated Atg of mitochondria is usually described as the core mechanism for regulating mitophagy in mammalian cells [Figure 2].[13] Both Pink1 and Parkin are linked to the pathogenesis of autosomal recessive juvenile Parkinsonism.[12,14] PARK2 (Parkin) is traced to a delicate site in chromosome 6q25-q26, which is usually eradicated in various human cancers, namely ovarian, breast, bladder, lung cancers, and others.[3] It is also involved in the regulation of mitochondrial morphology. Pink1 is a serine/threonine kinase that has a mitochondria-targeting signal in its N-terminus. After import into mitochondria through translocase of outer membrane and translocase of inner membrane complexes, Pink1 is anchored at the inner mitochondrial membrane (IMM).[15] In intact mitochondria, matrix processing proteases and peptidases continuously degrade Pink1.[16,17] However, in depolarized mitochondria, the import to the IMM is inhibited and Pink1 accumulates at the outer mitochondrial membrane (OMM).[12]

Once localized at the mitochondria, PINK1 phosphorylates Parkin at Ser 65[12] homologous to the site where ubiquitin was phosphorylated, which activates Parkin by inducing dimerization and an active state. This allows for Parkin-mediated ubiquitination on other proteins resulting in autophagic destruction of the dysfunctional organelles.

Parkin substrates at the OMM, include a number of proteins like VDAC1, MIRO, and Mfn-2.[3] Moreover, cells harboring VDAC1 knockout are characterized by the significant decrease of Parkin translocation to the mitochondria and generally decrease of mitophagy. Some of these substrates

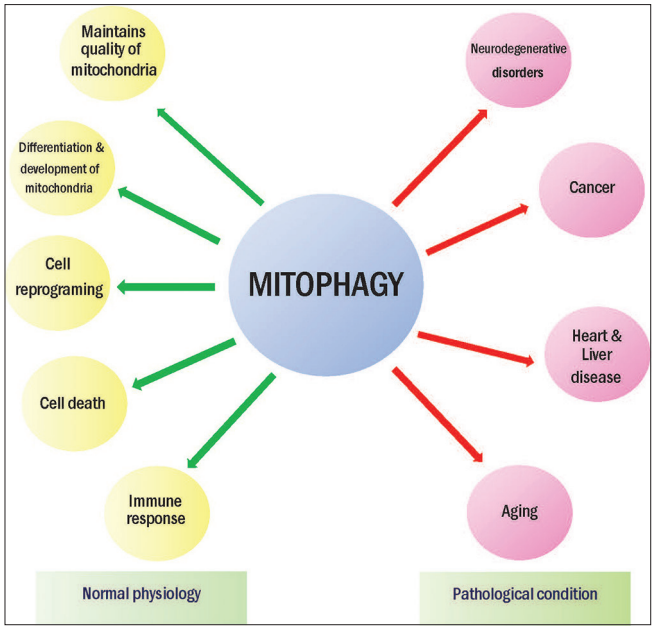

Figure 1: Various roles of mitophagy in normal physiology and pathological conditions

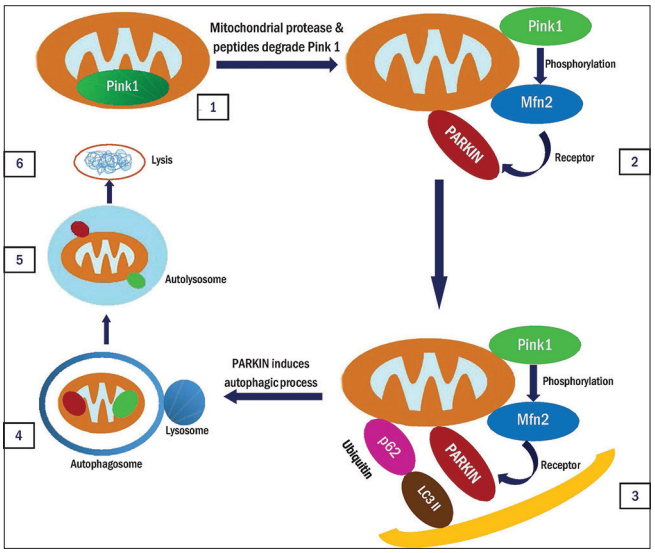

Figure 2: Mechanism of mitophagy mediated by pink1-parkin pathway 1 Pink1 is constitutively degraded in healthy mitochondria. 2 Accumulation of Pink1 at the outer membrane and recruits PARKIN and Mfn2 acts as a receptor for PARKIN on mitochondria 3 PARKIN ubiquitinates, p62, an OMM protein, which binds with LC3 (adapter protein), PARKIN, subsequently induces autophagy. 4-6 Mitochondria is subsequently degraded by the autophagic process

viz. ubiquitinated VDAC1, on being ubiquitinated by Parkin, create a docking site for LC3 interacting proteins p62/SQSTM1 and NBR-1, which allows selective degradation of mitochondria at the autophagosome, which is mediated by Parkin. The knockdown of p62 leads to a significant decrease of mitophagy.[18] According to other observations, p62 appears to be dispensable for mitophagy. p62 can induce mitochondrial clustering, following its recruitment by Parkin, but it occurs in a VDAC1-independent manner.[7]

Recruitment of Parkin to depolarized membranes is inhibited by the anti-apoptotic Bcl-XL, Mcl-1, and Bcl-W proteins in a Beclin-independent manner, although not by Bcl-2 itself. Direct interaction of Parkin with Bcl-XL, Mcl-1, and Bcl-W, inhibits mitophagy by blocking the interaction of Parkin with PINK1, thereby arresting the Parkin-dependent ubiquitination of mitochondrial targets. On the contrary pro-apoptotic BH3 proteins, namely Puma, Noxa, Bim, and Bad, excluding BH3 proteins like BNIP3, Nix, or Beclin1, enhanced Parkin translocation to mitochondria, possibly by reducing the interaction of Parkin with the Bcl-2-related molecules.[3,19]

Other alternate models defining the role of Parkin in mitophagy involve its function much more indirectly and incorporates mitophagy receptor AMBRA1. On induction of mitophagy, AMBRA1 translocates to the mitochondria, where it interacts with Beclin1 protein causing activation of Parkin independently of PINK.[20,21] According to other data, a fraction of AMBRA1 is constantly located to the OMM and is normally associated with Bcl-2 protein, but upon stimulation of mitophagy AMBRA1 is dislocated, binds to Beclin1 and then to Parkin.[22] The interaction of endogenous Parkin and AMBRA1 is strongly increased during prolonged mitochondrial depolarization. AMBRA1 rarely has a role for the translocation of Parkin to the depolarized mitochondria but plays an essential role for subsequent removal of mitochondria.[20] Several studies have suggested that upon mitophagy induction, AMBRA1 has the capability to bind to the autophagosome adapter LC3, exploiting the LIR domain. This interaction is crucial for the promotion of Parkin-dependent and–independent mitochondrial clearance.[7]

BNIP3, NIX

Other receptors involved in mitophagy are BNIP3 (BCL2/adenovirus E1B 19 kDa interacting protein 3) and its homolog, BNIP3/Nix [Figure 3]. They are BH3-only proteins and proapoptotic members of the Bcl-2 family. These mitophagy receptors, located at the OMM, can activate mitophagy in ubiquitinin-dependent manner.[23] BH3 domains of BNIP3 and Nix inhibit the anti-apoptotic function of Bcl-2 proteins converting them into pro-apoptotic proteins. BNIP3

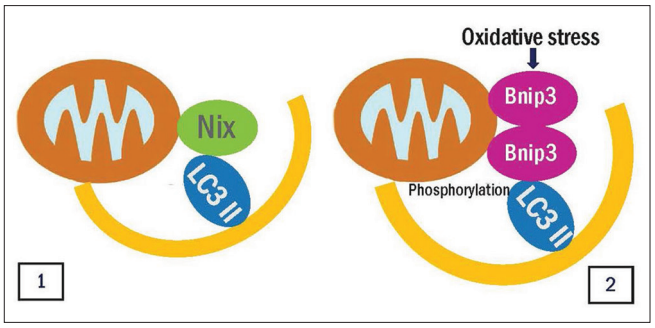

Figure 3: LC3-interacting molecules act as receptors for autophagosomes on mitochondria. 1-2, Nix and Bnip3, BH3-only proteins, interact with LC3 through LIR domain and regulate mitochondrial autophagy

and Nix have the same LIR domains; using these domains BNIP3 and Nix provide binding to LC3 on autophagosomes. Serine residues 17 and 24 after phosphorylation encircles BNIP3 LIR and promotes binding to specific Atg8 members LC3B and GATE-16. Therefore, phosphorylation of BNIP3 LIR stimulates either apoptosis or pro-survival mitophagy.[7]

FUNDC1

FUNDC1 is the type of receptor fixed on the OMM with its N-terminus facing the cytoplasm and contains the LIR domain that provides direct binding to LC3 under hypoxic conditions. However, during starvation, mitochondrial clearance is not dependent on FUNDC1, thereby suggesting its specificity for hypoxia-induced mitochondrial Atg.[15,24] Mutations in the LIR domain leads to disruption of its association with LC3 which prevents mitophagy.[24] FUNDC1 also behaves as a mitochondrial receptor for unc-51-like Atg-activating kinase 1. Mitochondrial Atg is promoted by unc-51-like Atg-activating kinase 1 which translocates to depolarized mitochondria and phosphorylates FUNDC1 at Ser 17.[15] In contrast to BNIP3 and NIX, FUNDC1 must be dephosphorylated by the mitochondrial phosphatase PGAM5 to cause mitophagy.[7] This dephosphorylation of FUNDC1 is essential for its interaction with LC3 and mitochondrial Atg, whereas CK2 negatively regulates mitochondrial Atg by phosphorylating the same residue of FUNDC1.[25]

Cardiolipin

Cardiolipin is a phospholipid of the IMM and translocates to the OMM in response to any mitochondrial injury. It interacts directly with LC3 in primary cortical neurons and SH-SY5H cells.[12] The inhibition of cardiolipin synthase or phospholipid scramblase-3 reduces the delivery of mitochondria to autophagosomes. Mutation of the residues, thought to be of cardiolipin interaction sites in LC3 inhibits mitochondrial Atg.[26]

General control of amino acid synthesis 5-like 1 (GCN5 L1)

Several evidences suggest that lysine acetylation controls a number of cellular functions, that includes Atg in response

to metabolic stress. Acetyl-CoA, an intermediate product of metabolic pathways, is a negative regulator Atg and during starvation, its level is thought to be diminished. Also, GCN5 L1 which is a part of the mitochondrial acetyltransferase mechanism, is downregulated, and sirtuin3, a mitochondrial deacetylase, is activated in HepG2 cells. Downregulation of GCN5 L1 diminishes acetylation of mitochondrial proteins and stimulates mitochondrial Atg, which in turn, slows down respiration and induces stress-resilience in cells. This mitochondrial Atg is affiliated with Atg5 as well as p62 but is independent of Parkin, thereby questioning the fact as to whether Atg regulated by GCN5 L1 is mitochondria selective or not.[12]

Mitophagy and mitochondria

The quality of mitochondria, which are highly dynamic organelles and changes morphology constantly is controlled by fusion and fission along with mitophagy.[7] Mfn1, Mfn2 localized on the OMM and Opa1 on the IMM regulates the fusion of mitochondria, whereas fission is regulated by Drp1 (dynamin 1-like), fission 1, and Miff.[27]

Fission inhibited by a dominant-negative form of Drp1 or by knockdown of fission 1, obstructs mitochondrial Atg and results in the accumulation of dysfunctional mitochondria.[12] Parkin promotes mitochondrial fission through ubiquitination and degradation of Mfn1 and Mfn2, which, in turn, increases mitophagy.[28] Ikeda *et al*. reported that genetic deletion of Drp1 obstructed general Atg as well as mitochondrial Atg in mice heart.[29] Kageyama *et al*. reported that Drp1 is required for Parkin-independent mitochondrial Atg in the heart and that Drp1 and Parkin act synergistically to promote mitochondrial homeostasis in the brain.[30] On the other hand it has also been reported that Drp1 ablation increases mitophagy and causes generalized loss of mitochondria.[12]

The role of mitochondrial fusion in regulating Atg is quite complex. Increase in the number of small, spherical mitochondria occurs due to downregulation of Mfn1,[31] whereas downregulation of Mfn2 increased pleomorphic and enlarged mitochondria in cardiomyocytes. Mfn1 and Mfn2 removed together in the adult heart resulted in mitochondrial fragmentation and respiratory dysfunction, that induced dilated cardiomyopathy.[32,33] Downregulation of Mfn2 inhibits Parkin-mediated mitophagy, whereas unopposed fission caused by either single or combined downregulation of Mfn1 and Mfn2 may positively affect nonselective Atg.[34] Therefore, the overall effects of Mfn1 and Mfn2 downregulation on mitochondrial clearance by Atg are unclear.[12]

The processes of fission, fusion, and mitophagy are interrelated. Interaction between Atg11 and Dnm1 is essential for mitophagy to progress while targeting this interaction severely hindered mitophagy.[35] As it is well-known that mitochondrial fission-fusion is a key regulator of cell proliferation and differentiation,[36] suppression of mitophagy will consequently alter the signaling components and the cell cycle machinery.[7]

Atypical mitochondrial clearance

Nishida *et al*. revealed that Atg5 and Atg7 double knockout cells are capable in forming autophagosomes and degrade autophagic substrates inside autolysosomes in response to certain stimuli.[37] During this process of Atg5/Atg7 independent Atg also known as alternative Atg, lipidation of LC3 does not occur. Instead, Rab9, which is a small GTPase associated with membrane trafficking and fusion between the trans-Golgi network and late endosomes, plays an important role in generating autophagosomes by promoting fusion of the phagophore with vesicles derived from the trans-Golgi network and late endosomes. Recently conducted studies reveal that unc-51 like Atg activating kinase 1 dependent, macro-Atg which is independent of Atg5 serves as the best method to remove mitochondria from reticulocytes during the final stages of maturation of erythrocyte.[38] Oxidative stress induces a vesicular transport pathway that selectively removes mitochondrial proteins for delivery to the lysosomes in COS7 cells. This mechanism does not require mitochondrial depolarization and is independent of Atg5 and LC3, thereby indicating its difference from Atg or selective mitophagy.[12,39]

Oxidative stress and hypoxia

Two important factors contributing to mitophagy are oxidative stress and hypoxic conditions. Both of these have the capability to deteriorate mitochondrial functions and structure. Oxidation of mitochondrial substrates is often linked to the seepage of electrons from the respiratory chain and the formation of RONS. Excessive production of RONS may result in oxidative damage to the mitochondrial proteins, lipids, and DNA. RONS arises mainly as byproducts of mitochondrial respiration due to electron leakage from the damaged respiratory chain. Therefore, under extreme oxidative stress, mitochondria become both the source as well as the target of RONS.[7] Production of RONS by impaired mitochondria stimulates transcription of the PINK1 gene by activation of nuclear factor (erythroid-derived 2)-like 2 (NRF2), an antioxidant transcription factor. Antioxidants or overexpression of KEAP1, a potent inhibitory partner to NRF2, restricts PINK1 expression induced by activated NRF2 and inhibits mitophagy.[40] On the other hand, RONS has the capability to inactivate Parkin, which results in blocking of mitophagy. Depending on the severity, oxidative stress either promotes mitophagy, facilitating cell survival, as mitochondria posing a threat to the cell gets

eliminated, or suppress it. Stimulation of mitophagy by RONS can be prevented by antioxidants. Studies conducted have revealed that mitophagy caused by the cultivation of cells in nutrient-deficient medium was prevented by the addition of antioxidant N-acetylcysteine.[7,41] Treatment of cells with the inhibitor of mammalian target of rapamycin (mTOR) rapamycin resulted in enhanced reactive oxygen species (ROS) production and mitochondrial lipid oxidation, which was blocked using the antioxidant resveratrol.[42]

Hypoxia too is another stressful condition that compromises mitochondrial function and might cause damage to the organelles. Low level of oxygen leads to stabilization of Hypoxia Inducible Factor 1α (HIF1α), which is responsible for upregulation of a number of genes facilitating cell adaptation to new environmental conditions.[7,43] Hypoxia stimulates expression of mitophagy receptors BNIP3 and NIX as they contain Hypoxia Responsive Elements at the promoter region.[44,45] In addition to the reduced oxygen level, HIF1α stabilization may also be caused by the deficiency of iron. Chelation of iron results in PINK1/Parkin mediated mitophagy, thereby confirming the participation of HIF1 in mitophagy regulation.[7,46]

MITOPHAGY AND CANCERS

Dysregulation of mitochondrial function and accumulation of mitochondrial DNA (mtDNA) mutations are frequently observed in human cancers. Several recent studies suggest that functional loss of mitophagy regulators is closely linked to cancer development and progression. The close relationship between mitophagy and cancer is evident through the regulation of expression of Parkin, BNIP3, NIX, and others by tumor suppressors, namely p53 and Rb and by oncogenes such as NF-κB, FOXO3, and HIF-1α.[3] Based on this notion, recent studies conducted suggest that Parkin is a potential tumor suppressor. Parkin is located on chromosome 6q25-q27 that is frequently deleted in cancer.[47-49] Another mitophagy effector, PINK1, induced a decrease in cell growth in soft agar when overexpressed in MCF-7 cells. PINK1 mRNA expression has also been proposed to serve as a survival prognostic marker in adrenocortical tumors.[50-54]

Mitophagy receptor BNIP3 is suppressed in pancreatic cancer and hepatocellular carcinoma. It is assumed that the activity of BNIP3 as a mitophagy receptor protects cells from malignant transformation by controlling the RONS level and prevention of HIF1 stabilization. Exposure to carcinogens leads to loss of BNIP3, accumulation of damaged mitochondria, increased RONS production, enhanced genomic instability, and progression of more severe forms of pancreatic cancer.[54] Elevated mitochondrial RONS increase the expression of HIF1 and HIF target genes, including those involved in glycolysis and angiogenesis two processes that are also markedly increased in BNIP3-null tumors. These studies thereby show that dysfunction of mitochondria due to defects in mitophagy has the capability to promote Warburg effect and tumor progression.[7,55] NIX/BNIP3 L (BNIP3-like protein) expression is a factor of good prognosis for astrocytomas (AS, grade II). In hepatocellular carcinomas, BNIP3 L and BNIP3 silencing has been linked to a poor prognosis.[56] Interestingly, the silencing of these genes in these tumors has been correlated to hypermethylation.[51]

Maintaining mitochondrial quality control is of utmost importance, as dysfunctional mitochondria may lead to the accumulation of ROS,[57] that could damage nuclear DNA as well as mtDNA, inducing genome instability and tumor initiation.[51] Studies have also revealed that an increase of mitophagy in cancer cells promotes survival and adaption in microenvironments. Hypoxia is commonly associated with solid tumors. The removal of mitochondria is important to lower ROS generation and maintain oxygen homeostasis. It has been reported that HIF1 , which plays an important role in the adaptation and survival of cancer cells to hypoxic condition, induces the expression of BNIP3.[58] Therefore, it is suggested that the increase of mitophagy is an adaptive response to hypoxia to promote the survival of cancer cells.[45] As such, increase in resistance of cancer cells may be an important factor in promoting the progression of cancer cells thereby consequently increasing metastasis. Overall, the role of mitophagy in cancer development seems rather complex. While the expression of mitophagy regulatory genes is reduced in a variety of cancers, the activation of these genes leads to cancer cell proliferation and tumor growth.[47]

MITOPHAGY AND ANTICANCER THERAPY

Cancer involves abnormal cell growth which has the potential to invade and spread to parts of the body. Therefore, stimulation of various modalities of cell death could provide a new avenue in the treatment of cancer. Mitophagy, can facilitate cell survival by adapting to stressful conditions or cause cell death due to the excessive removal of mitochondria. Therefore, targeting the pathways of mitophagy might affect the balance between tumorigenesis and cell death. Scientific studies and researches are being conducted to develop drugs that selectively affect mitophagy, which could stimulate the elimination of tumor cells. Thus, mitophagy inducers and inhibitors may be equally effective in anticancer therapy.[7]

For instance, the linamarase, linamarin, and glucose oxidase (lis/lin/GO) killer-suicide system has been recognized as a robust mitophagy trigger to induce cell death and growth inhibition of human cancer cells both *in vitro* and *in vivo*.[59,60] Another striking example demonstrating the efficacy of mitophagy induction for cancer therapy is ceramide, which acts as a bioactive sphingolipid to induce cell death, growth inhibition, and senescence in various human cancer cells.[65,66] Interestingly, recent studies suggest that ceramides can promote cell death and tumor regression by inducing mitophagy.[59, 61]

Several recent studies suggest that low-intensity ultrasound therapy along with curcumin enhances the cell death of nasopharyngeal carcinoma CNE2 cells by initiating mitophagy. Therefore, the induction of cell death by combined treatment triggers mitophagy, which is another potential and feasible method for treating malignancies.[59,62]

Due to the adaptive nature of mitophagy to several stress factors, its inhibition also represents an effective strategy for anticancer therapy. In many cases, targeting mitophagy enhanced the effect of anticancer drugs. For example, PINK1 inhibition by RNA interference technology made cells more sensitive to conventional chemotherapy.[7,63]

Doxorubicin, a DNA damaging agent, is thought to cause toxicity by inducing mitochondrial dysfunction and enhancing superoxide formation[64-66] Salinomycin, an antibacterial and coccidiostat ionophore drug, also has a potent anticancer role through mitochondrial hyperpolarization.[64,67]

The number of mitophagy inhibitors till date is considerably less compared to that of inducers [Table 1]. Cyclosporine A prevents mitophagy by decreasing the permeability of the OMM. It acts through binding to cyclophilin D that is a part of nonspecific Ca2þ stimulated mitochondrial pores.[68] A group of inhibitors includes mitochondrial division inhibitor-1 that inhibits the Drp-1-GTPase, thereby disrupting the mitochondrial fragmentation process.[7,69] Another known inhibitor of mitophagy is liensinin. It was shown that this agent enhanced breast tumor cells sensitivity to doxorubicin both *in vitro* and *in vivo*.[70] These facts suggest that the engagement of mitophagy inhibitors in combination with conventional cancer treatment can markedly improve the effectiveness of chemotherapy.

ORAL SQUAMOUS CELL CARCINOMA AND MITOPHAGY

Dichloroacetate (DCA), an inhibitor of the pyruvate dehydrogenase kinase, boosts oxidative phosphorylation, by stimulating mitochondrial oxidation of pyruvate. At relatively high doses, Ruggieri *et al.* reported a distinctive pro-apoptotic effect in oral squamous cell carcinoma derived cells, specifically characterized by a glycolysis-dependent metabolism.[71] This effect was associated with the overproduction of ROS and to extensive modifications of mitochondrial networking. Analysis of the effect of DCA on the mitochondrial dynamics showed a significant increase of the pro-fission protein Drp1 in DCA-treated OSCC cells. Moreover, a dose-response increase of the Atg marker LC3-II and the degradation of the mitochondrial protein Tom20 were revealed. Consistently, electron microscopy analysis of DCA-treated cells unveiled the occurrence of autophagosomes containing mitochondria and of cristae remodeling. Most notably, the above reported DCA-mediated effects were specifically attained in more glycolytic OSCC cell lines. Therefore, the findings suggest that DCA is able to promote mitophagy likely via Drp1-mediated fission thereby (de)regulating the mitophagic clearance.[72] Therefore, these observations emphasize the relevance of mitochondrial morpho-functional analysis and help to determine the targeting and mechanism of action of anti-cancer metabolic drugs.

MELATONIN AND MITOPHAGY

Mitophagy can facilitate the death of tumor cells due to excessive removal of mitochondria. Shen *et al.* hypothesized that melatonin may induce apoptosis as well as Atg in head

Table 1: Inducers and inhibitors of mitophagy and their functions

Inducers	Function	Inhibitors	Function
Cadmium chloride	Stimulates ROS production	lis/lin/GO	Inhibition of cytochrome c oxidase
1,10-phenanthroline	Stimulates Drp1- dependent fragmentation of mitochondria	MDIVI-1	Inhibits DRP1
C_{18}-ceramide (C_{18}-Pyr-Cer)	Targets autophagosomes to mitochondria	Liensinine	It blocks the fusion of autophagosome-lysosome
Deferoxamine, Deferiprone	Iron chelators	Cyclosporine A	Inhibits mitochondrial permeability transition pore opening
PMI (P62-mediated mitophagy compound)	Mitophagy occurs due to stimulation in expression of p62, without affecting the mitochondrial membrane potential		
Salinomycin	Mitochondrial depolarization		

ROS: Reactive oxygen species, Lis: Linamarase, Lin: Linamarin Go: Glucose oxidase, MDIVI-1: Mitochondrial division inhibitor-1

and neck squamous cell carcinoma (HNSCC) by determining the levels of the mitophagy-related proteins LC3-II and Nix. Activation of AKT mTOR signaling pathway induces HNSCC.[73]

DISCUSSION

Recent advancement in molecular mechanisms of mitophagy, including recognition of damaged mitochondria and their engulfment by autophagosomes, has improved our understanding of the quality control mechanisms in mitochondria. However, our knowledge regarding mitophagy in oral cancers is very limited. Further research is required to confirm the significance of Pink1/Parkin, Bnip3, Nix, FUNDC, and cardiolipin pathways, and the protein kinases, such as ULK1/2, AMPK, mTOR and CK2 in oral cancers.

Mitochondria in tumor cells differ from those in normal cells. Tumor cells reduce the number of mitochondria in response to hypoxia, lack of nutrients, or elevated ROS levels. Hence, mitophagy provides a new dimension in the selective elimination of tumor cells, which could be targeted for developing new anticancer drugs. A recent study states that DCA, an inhibitor of the pyruvate dehydrogenase kinase promotes mitophagy by Drp1-mediated fission, regulating mitophagic clearance in oral cancers, thereby emphasizing the relevance of mitochondrial morpho-functional analysis and determining the target and mechanism of anti-cancer metabolic drugs.

CONCLUSION

Mitophagy is a double-edged sword in cancer cell biology, and the regulation of this process could promote both cancer cell death and survival. Inhibition of mitophagy along with chemotherapeutic agents seems to be more suitable in the treatment of various cancers. Further studies and analysis are required to know the regulation of mitophagy in different cancer types and in anticancer therapy, which may open new avenues and strategies for the treatment of cancer.

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Conflicts of interest

There are no conflicts of interest.

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