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Autophagy-targeted therapy to modulate age-related diseases: Success, pitfalls, and new directions

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ABSTRACT

Autophagy is a critical metabolic process that supports homeostasis at a basal level and is dynamically regulated in response to various physiological and pathological processes. Autophagy has some etiologic implications that support certain pathological processes due to alterations in the lysosomal-degradative pathway. Some of the conditions related to autophagy play key roles in highly relevant human diseases, e.g., cardiovascular diseases (15.5%), malignant and other neoplasms (9.4%), and neurodegenerative conditions (3.7%). Despite advances in the discovery of new strategies to treat these age-related diseases, autophagy has emerged as a therapeutic option after preclinical and clinical studies. Here, we discuss the pitfalls and success in regulating autophagy initiation and its lysosome-dependent pathway to restore its homeostatic role and mediate therapeutic effects for cancer, neurodegenerative, and cardiac diseases. The main challenge for the development of autophagy regulators for clinical application is the lack of specificity of the repurposed drugs, due to the low pharmacological uniqueness of their target, including those that target the PI3K/AKT/mTOR and AMPK pathway. Then, future efforts must be conducted to deal with this scenery, including the disclosure of key components in the autophagy machinery that may intervene in its therapeutic regulation. Among all efforts, those focusing on the development of novel allosteric inhibitors against autophagy inducers, as well as those targeting autolysosomal function, and their integration into therapeutic regimens should remain a priority for the field.

1. Introduction

Autophagy is a major intracellular degradation system responsible for the maintenance of bioenergetic homeostasis, cell survival, cell differentiation, organism development, and cell death regulation (Yang and Klionsky, 2020). In mammalian cells, there are three types of autophagy, microautophagy, chaperone-mediated autophagy (or CMA), and macroautophagy (Parzych and Klionsky, 2014). Microautophagy is used to describe the direct engulfment of cargo by invagination of the lysosomal membrane, while CMA uses a chaperone and a lysosomal transmembrane protein for direct translocation of some proteins with the KFERQ motif into the lysosomal lumen (Parzych and Klionsky, 2014). Finally, macroautophagy (hereinafter autophagy) is a specialized vesicular transport in which cargoes are transported to lysosomes for degradation (Yu et al., 2018). This cellular degradation process is capable of breaking even entire organelles, through specific molecular mechanisms e.g., mitophagy (mitochondria), pexophagy (peroxisomes), ERphagy (endoplasmic reticulum), ribophagy (ribosomes), and nucleus (nucleophagy) (Kirkin and Rogov, 2019).

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List of abbreviatures

β-CTF	β-C-terminal fragment
3-MA	3-methyladenine
ABL1	ABL Proto-Oncogene 1, non-receptor tyrosine kinase
AD	Alzheimer's disease
ADIPOR1	Adiponectin receptor 1
AKT	AKT Serine/Threonine Kinase
ALS	Amylotrophic lateral sclerosis
AMBRA1	Autophagy and beclin-1 regulator 1
AMK	Activated protein kinase
APP	amyloid β-precursor protein
ATG	Autophagy-related
ATG10	Autophagy related 10
ATG101	Autophagy Related 101
ATG12	Autophagy related 12
ATG13	Autophagy related 13
ATG14L	Autophagy Related 14
ATG15	Autophagy related 15
ATG16L1	Autophagy related 16 like 1
ATG3	Autophagy related 3
ATG4B	Autophagy Related 4B Cysteine Peptidase
ATG5	Autophagy related 5
ATG7	Autophagy related 7
ATG9	Autophagy related 9
ATP	Adenosine triphosphate
ATP2/SERCA	Sarcoplasmic/endoplasmic reticulum calcium ATPase
AUTEN-67	1-{3- [(4-nitrobenzenesulfonyl)azanidyl]-1,4-dioxo-1,4-dihydronaphthalen-2-yl}-3H-1,3-benzodiazol-1-ylium
AZD8055	5- [2,4-bis [(3S)-3-methylmorpholin-4-yl]pyrido [2,3-d] pyrimidin-7-yl]-2-methoxyphenyl methanol
BCR	BCR activator of RhoGEF and GTPase
BMI1	BMI1 proto-oncogene, polycomb ring finge
BNIP3	BCL2 interacting protein 3
BNIP3L	BCL2 interacting protein 3 like
BRAF	B-Raf proto-oncogene, serine/threonine Kinase
CaMKKβ	Calcium/calmodulin-dependent protein kinase beta
CQ	Chloroquine
CTRP9	C1q/tumor necrosis factor-related protein-9
CVD	Cardiovascular disease
DEPTOR	DEP domain-containing mTOR-interacting protein
DFCP1	Double FYVE-Containing Protein 1
EGFR	Epidermal growth factor receptor
ER	Endoplasmic reticulum
FATC	FAT domain at C terminus
FDA	US Food and Drug Administration
FIP200	FAK family kinase-interacting protein of 200 KDa
FKBP	FK-506 binding protein
FKBP12	12 kDa FK506-binding protein
FUNDC1	FUN14 domain containing 1
GLP1R	Glucagon-Like Peptide 1 Receptor
GSK-3β	Glycogen synthase kinase 3β
GSα	Calpain–G-stimulatory protein α
HCQ	Hydroxychloroquine
HD	Huntington's disease
HSC70	Heat shock protein family A (Hsp70) member 8
IGFR	Insulin/insulin-like growth factor receptor
IP3	Inositol 1,4,5-trisphosphate
KRAS	KRAS proto-oncogene, GTPase
LAMP2A	Lysosomal associated membrane protein 2
LC3	MAP1 light chain 3-like protein 1
LKB1/STK11	Serine/threonine kinase 11
mLST8	mammalian lethal with Sec13 protein 8, also known as GβL
mTOR	Mechanistic target of rapamycin kinase
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NBR1	NBR1 autophagy cargo receptor
NDP52/CALCOCO2	Calcium binding and coiled-coil domain 2
OPTN	Optineurin
P62/SQSTM1	Sequestosome 1
PARP	Poly (ADP-ribose) polymerase
PD	Parkinson's disease
PDK1	3-phosphoinositide-dependent protein kinase 1
PE	Phosphatidylethanolamine
PHB2	Prohibitin 2
PI3K	Phosphatidylinositol 3-kinase
PI3KC2α	Phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha
PI3KC2β	Phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta
PI3KC2γ	Phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma
PI3KCα	Phosphatidylinositol-4,5-bisphosphate 3-Kinase catalytic subunit alpha
PI3KCβ	Phosphatidylinositol-4,5-bisphosphate 3-Kinase catalytic subunit beta
PI3KCγ	Phosphatidylinositol-4,5-bisphosphate 3-Kinase catalytic subunit gamma
PI3KCδ	Phosphatidylinositol-4,5-bisphosphate 3-Kinase catalytic subunit delta
PI3P	Phospholipid phosphatidylinositol3-phosphate
PIKK	PI3K-related kinase
PIP2	phosphatidylinositol 4,5-bisphosphate
PIP3	phosphatidylinositol 3,4,5-trisphosphate
PPT1	Palmitoyl-protein thioesterase 1
PRAS40	Proline-rich AKT substrate, 40 KDa
PRR5	Proline-rich protein 5
PRR5L	Proline-rich protein 5-like, also known as protor1 and protor2
RAGE	Receptor for advanced glycation end products
RB1	RB transcriptional corepressor 1
rCTRP9	Recombinant CTRP9
Rhebs	Ras Homolog, mTORC1 bindingGTPase in the Ras family
RICTOR	RPTOR independent companion of mTOR complex 2
RUBCN	Rubicon autophagy regulator or beclin-1 interaction protein-containing cysteine-rich domain
SCA	Spinocerebellar ataxia
SFK	Src family kinase
SIN1	Stress-activated map kinase (SAPK)-interacting 1
SIRT1	Sirtuin 1
STX17	Syntaxin 17
TAX1BP1	Tax1 binding protein 1
TFEB	Transcription factor EB
TP53	Tumor protein P53
TRIM5	Tripartite motif containing 5
TSC1	TSC complex subunit 1
TSC2	TSC complex subunit 2
ULK1	Unc-51-Like like Kinase kinase 1
ULK2	Unc-51-Like like Kinase kinase 2
UVRAG	Ultraviolet irradiation resistance-associated gene
V-ATPase	Vacuolar-type H^+-ATPase
VPS15	Phosphoinositide-3-Kinase, Regulatory Subunit 4, P150
VPS34	Phosphatidylinositol 3-Kinase Catalytic Subunit Type 3
WIPI	WD Repeat Domain, Phosphoinositide Interacting

The deterioration of autophagy favors several pathological processes due to alterations in the lysosomal degradation pathway, e.g., cell malignancy, heart failure or hypertrophy, and neurodegeneration (Mulcahy Levy and Thorburn, 2020; Nishida and Otsu, 2016; Corti et al., 2020; Saha et al., 2018). Cardiovascular diseases (15.5%), malignant and other neoplasms (9.4%), and neurodegenerative diseases (3.7%) are the leading cause of health disability as estimated by the Global Burden of Disease (Global Health Estimates Technical Paper WHO/HIS/IER/GHE/2018.3, 2018). According to the DALYs (disability-adjusted life years) report, 31.2% of the diseases with the highest mortality (832 million of the 2669 million) are attributed to the aging process, especially in high- and middle- income regions (Global Health Estimates Technical Paper WHO/HIS/IER/GHE/2018.3, 2018). There is a consensus understanding that pharmacologic or genetic modulation of autophagy might recover the functionality of diseased cells, and attenuate clinical relapses (Yang and Klionsky, 2020). Undeniably, modulation of autophagy for therapeutic purposes must consider its role in human etiopathology. While its enhanced activation is related to pathological cardiac remodeling, its degradative failure leads to neurodegeneration and tumorigenesis (Galluzzi et al., 2017a). Herein, we discuss the pitfalls and success in regulating autophagy initiation and the lysosome-dependent pathway to address targeted therapy to cancer, neurodegenerative and cardiac diseases.

2. The autophagy pathway

Under physiological conditions, autophagy acts as a catabolic process regulated by the two main cellular sensors for nutrition and energy, the kinases mTOR and AMPK, respectively (Kim et al., 2011a). mTOR is part of two functionally and biochemically distinct complexes: the rapamycin-sensitive mTOR complex 1 (mTORC1) and the rapamycin-insensitive mTOR complex 2 (mTORC2) (Fig. 1).

mTORC1 consists of mTOR, together with RAPTOR, mLST8, PRAS40, and DEPTOR (Laplante and Sabatini, 2012). Structurally, mTOR that is common to mTORC1 and mTORC2, contains 2,549 amino acids that comprise distinct domains. The N-terminus region contains two tandemly repeated HEAT motifs composed of Huntingtin, elongation factor 3 (EF3), a subunit of protein phosphatase 2A (PP2A), and TOR1. After the HEAT region domain, there is a FAT-carboxy terminal domain (FAT) responsible for the interaction of mTOR with other proteins, an FKBP12-rapamycin binding domain termed FRB, and a catalytic kinase domain. In the C-terminus of mTOR protein is located a FRAP–ATM–TRAP domain, known as FATC, capable of sensing cytosolic regulatory signals for mTOR degradation (Thoreen et al., 2009). The inhibitory subunit PRAS40 is not present in the mTORC2 complex that contains mTOR, RICTOR, mLST8, PRR5 (also known as protor1), PRR5L (also known as protor2), and DEPTOR, as well as the regulatory subunit mSIN1

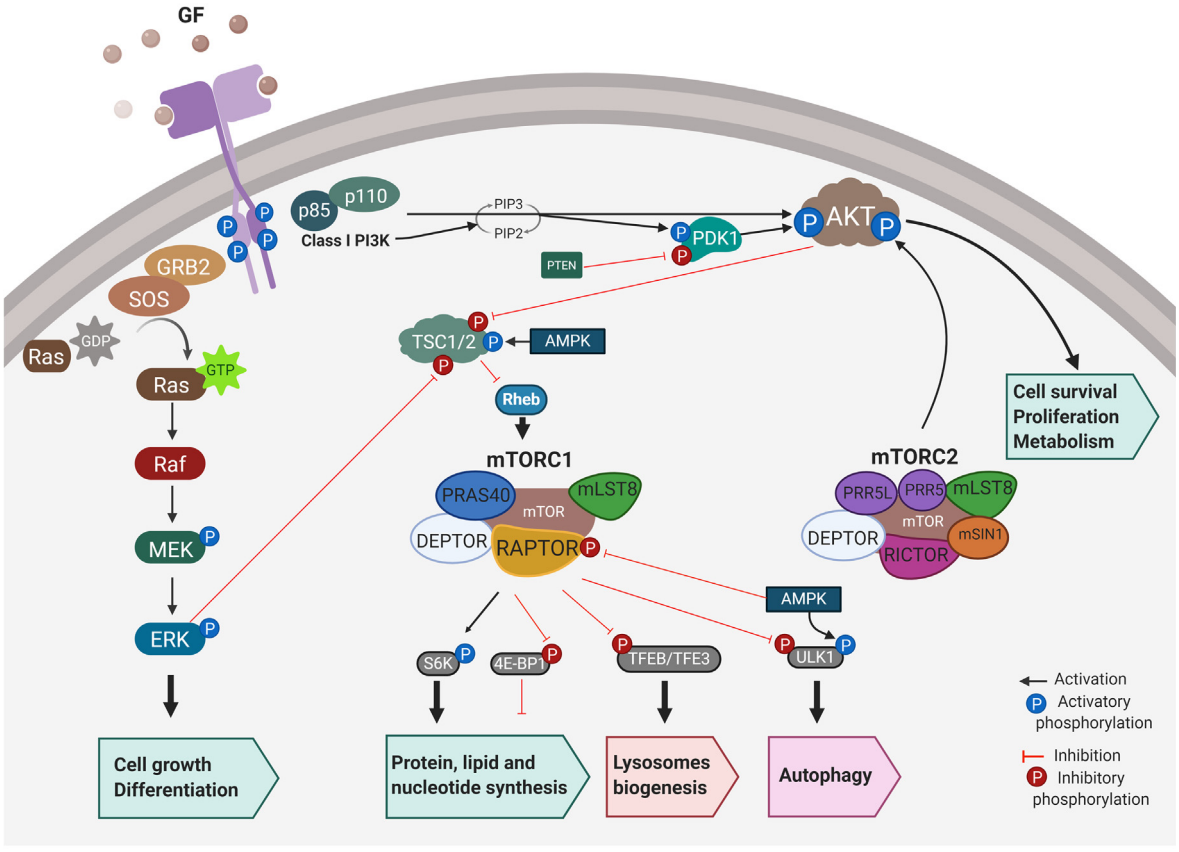

Fig. 1. Overview of the PI3K/AKT/mTOR pathway. Depending on upstream and downstream regulators of these networks' autophagy may be activated or inhibited. Growth factors (e.g., cytokines and hormones) induce PI3K/AKT signaling process by binding and activating the receptor tyrosine kinases or G-protein-coupled receptors. AKT phosphorylation by PDK1 can be modulated by either (PI3K Class I) and (PTEN) proteins, allowing it to become activated or inactivated, respectively. For instance, berberine inhibits PTEN expression that leads to increased AKT phosphorylation responsible for downstream phosphorylation of mTOR and consequent autophagy inhibition (Wang et al., 2020a). Aside from PDK1, mTORC2 also positively regulates AKT. When active, AKT can relieve the TSC1/2 complex towards Rheb to stimulate the kinase activity of mTORC1 and consequent promotion of protein, lipid, and nucleotide synthesis. On the other hand, AMPK phosphorylates the TSC1/2 complex with consequent Rheb inhibition and mTORC1 activity lessening, which leads to the initiation of autophagy and lysosomes biogenesis. Aside from AKT and AMPK, ERK also represents a promising target for the regulation of mTORC1. The proteins shown in the figure are not drawn to scale. For more details in the mTOR pathway see (Saxton and Sabatini, 2017). Figure created with BioRender.com.

(Fig. 1). While the stimulation of mTORC2 is poorly understood, since it is activated only by growth factors, mTORC1 senses and integrates several intracellular and extracellular signals, being capable of promoting anabolic processes, and inhibiting catabolic processes, such as autophagy (Shimobayashi and Hall, 2014). Thus, mTORC1 may constitute an early means of limiting autophagy signaling in favor of maximizing the synthesis of lipids, proteins, and nucleic acids for cell growth and metabolism, especially under conditions of nutrient availability. For this reason, it represents the most common pharmacological target to modulate autophagy.

In a favorable nutritional condition, mTORC1 inhibits the autophagy flux employing several inhibitory phosphorylations on the members of the ULK1 complex (composed by ULK1, ATG13, ATG101, and FIP200) which is the first complex that stimulates autophagosome biogenesis. In response to amino acid deprivation, mTORC1 interacts with Rag GTPases and induces their subsequent translocation to a membrane-bound compartment in lysosomes that contains the small RAS family GTPase Rheb. In its triphosphate state, Rheb is capable of activating mTORC1 in a process that is regulated by the GAP (GTPase-activating protein) activity of the TSC1/TSC2 complex (Long et al., 2005) (Fig. 1). In the case of growth factors, after activation of tyrosine kinase receptors, a phosphorylation cascade occurs mediated by class I PI3Ks translocated to the inner layer of the plasma membrane. As we discussed throughout the review, the PI3K family is a well-known pharmacologic target for positively regulating the autophagy machinery.

The PI3K family is composed of three different classes: Class I, Class II, and Class III. Class I PI3Ks are heterodimeric kinases composed of a catalytic subunit p110 (α, β, γ, or δ) and a regulatory subunit (p85α, p85β, p55γ, p101 or p84). Based on the catalytic subunits the Class I PI3Ks are further subdivided into class IA (with PI3KCα, PI3KCβ, or PI3KCδ) and class IB (with PI3KCγ). Unlike Class I PI3K, Class II comprises monomeric PI3Ks, including the three isoforms PI3KC2α, PI3KC2β, and PI3KC2γ (Jean and Kiger, 2014). Both Classes I and II PI3Ks are downstream effectors of receptor tyrosine kinases (e.g., IGF1R) and G-protein-coupled receptors (e.g., GLP1R). The Class III PI3K is a heterodimeric kinase composed of catalytic subunit type 3 (PIK3C3 or VPS34) and regulatory subunit 4 (PIK3R4 or VPS15/P150), which participates in autophagy nucleation (PI3K complex I) and autophagosome maturation (PI3K complex II) (Yu et al., 2018; Jean and Kiger, 2014; Ohashi et al., 2019). Then, for tyrosine kinases receptors, Class I PI3K is activated and phosphatidylinositol-4,5-bisphosphate (PIP2) is phosphorylated to phosphatidylinositol (Yu et al., 2018; Kirkin and Rogov, 2019; Mulcahy Levy and Thorburn, 2020)-trisphosphate (PIP3) leading to the recruitment of proteins bearing PH domains (e.g., AKT) and attachment to the PIP3-rich region on the plasma membrane together with another phosphoinositide-dependent protein kinase - PDK1. After being phosphorylated, PDK1 mediates complete activation of both AKT1 and AKT2 which in turn inhibit TSC1/TSC2,leading to positive phosphorylation activity of Rheb over mTORC1 (Gonzalez and McGraw, 2009). Furthermore, PTEN negatively regulates PI3K/AKT/mTOR networks through dephosphorylation of PDK1 (Fig. 1) (Gonzalez and McGraw, 2009).

When the activity of the serine/threonine kinase mTORC1 is suppressed due to signals of energy and metabolic stress (e.g., starvation, lack of growth factors, or decreased ATP levels) the ULK1 complex is no longer repressed, and autophagy is triggered. Additionally, mTORC1 inhibition triggers the expression of several genes related to the autophagy/lysosome pathway by nuclear translocation of the transcription factor TFEB (Di Malta et al., 2019). The ULK1 complex can alternatively be activated by AMPK (Kim et al., 2011a; Zachari and Ganley, 2017; Grasso et al., 2018). AMPK is composed of a catalytic α subunit and two regulatory molecules, the β and γ subunits. Under low energy conditions, LKB1/STK11 phosphorylates and activates AMPK, which in turn downregulates cellular anabolic processes and induces catabolic ones such as the autophagy pathway. Activated AMPK, using various phosphorylation, directly activates the ULK1 complex. Moreover, AMPK also promotes the activity of the ULK1 by activation of the TSC1/TSC2 complex and direct inhibition of mTORC1 (Kim et al., 2011a; Zachari and Ganley, 2017; Grasso et al., 2018) (Fig. 1).

The activated ULK1 complex translocates to discrete areas of the ER membrane where it recruits the Class III PI3K complex I (ATG14L, Beclin 1, VPS34, VPS15) initiating nucleation of the autophagosome, in which AMBRA1 plays a fundamental role in Beclin 1 interaction with the lipid kinase VPS34 (Fig. 2). As the nucleation process evolves, the PI3P aggregates mediated by the PI3K complex I are recognized by PI3P-binding proteins, such as the WIPI (mainly WIPI1 and WIPI2) and DFCP1 proteins (Grasso et al., 2018; Itakura and Mizushima, 2010; Axe et al., 2008). The clustering of PI3P with these proteins lead to changes in the ER membrane at the initiation site, forming a tiny structure called omegasome that is further elongated into a cup-shaped double-membrane structure, called phagophore that emerges in the cytoplasm through the mediation of many ATG proteins (autophagy-related proteins) (Grasso et al., 2018; Itakura and Mizushima, 2010). The unique multi-transmembrane ATG9 protein is also recruited to the site in a ULK1-dependent manner. The essential recruitment of ATG9-positive vesicles is believed to provide membrane components to the phagophore (Orsi et al., 2012; Karanasios et al., 2016) (Fig. 2).

During membrane elongation, and after ATG4B-mediated cleavage, LC3-I is lipidated with phosphatidylethanolamine (LC3-II) and anchored to autophagosomal membranes through a series of ubiquitin-like reactions involving ATG7, ATG3, and the complex ATG5-ATG12-ATG16L. LC3-II is essential for the biogenesis, expansion, and closure of the autophagosomal membrane, but also it plays a pivotal role in the selective cargo recognition, as well as in the fusion events with lysosomes (Grasso et al., 2018; Shpilka et al., 2012; Mohan and Wollert, 2018). The isolation membrane further elongates and wraps organelles and macromolecules, maturing into a double-membrane vesicle, called the autophagosome. As reviewed by Galluzzi et al. (2017b) most receptors related to autophagy (e.g., ATG34, ATG19, ATG32, BNIP3, BNIP3L, FUNDC1, NBR1, NDP52/CALCOCO2, OPTN, PHB2, P62/SQSTM1, TRIM5, and TAX1BP1) evolutionarily have a conserved region that allows them to interact with LC3 and, in turn, causes specific substrates to be engulfed into autophagosomes. Eventually, autophagosomes fuse with lysosomes to degrade engulfed material by the action of acid-dependent lysosomal hydrolases, e.g., cathepsins (Fig. 2).

Autophagy is a cellular program with a cytoprotective and pro-survival function, but it can also trigger regulated cell death (Galluzzi et al., 2017b). The dichotomy of these pro-survival and pro-death roles may be related to the extent and duration of autophagy, depending on the context of physiologic and/or pathological states. This means that autophagy is a double-edged sword and its potential as a therapeutic target depends on the context of each tissue and disease. Even with huge potential, until now, no intervention designed specifically for the autophagy machinery is clinically accessible to treat age-related diseases (Galluzzi et al., 2017a). However, there are some old repurposing drugs capable of regulating autophagy in cancer, neurodegenerative, and cardiac disorders, as we discuss in the following sections.

3. Modulation of autophagy as cancer therapy

Human cancer is a multifactorial disease with notable morbidity, being one of the most relevant public health issues worldwide (Ferlay et al., 2015), with an estimated global incidence of more than 27 million in 2030 (Boyle, 2008). During the next 10 years, people will suffer more death from cancer than from other more common diseases (Mathers and Loncar, 2006). To deal with such a high rate, 20,440 interventional clinical trials have been conducted, according to *Clinical Trials.Gov* (National Institutes of Health, 2016).

Cancer development consists of a multistep process, i.e., initiation, promotion, and progression, which involve irreversible genetic alterations or reversible epigenetic modifications in normal cells. Throughout the early stage of tumorigenesis, cancer cells acquire additional genetic abnormalities such as several chromosomes alterations (translocations,

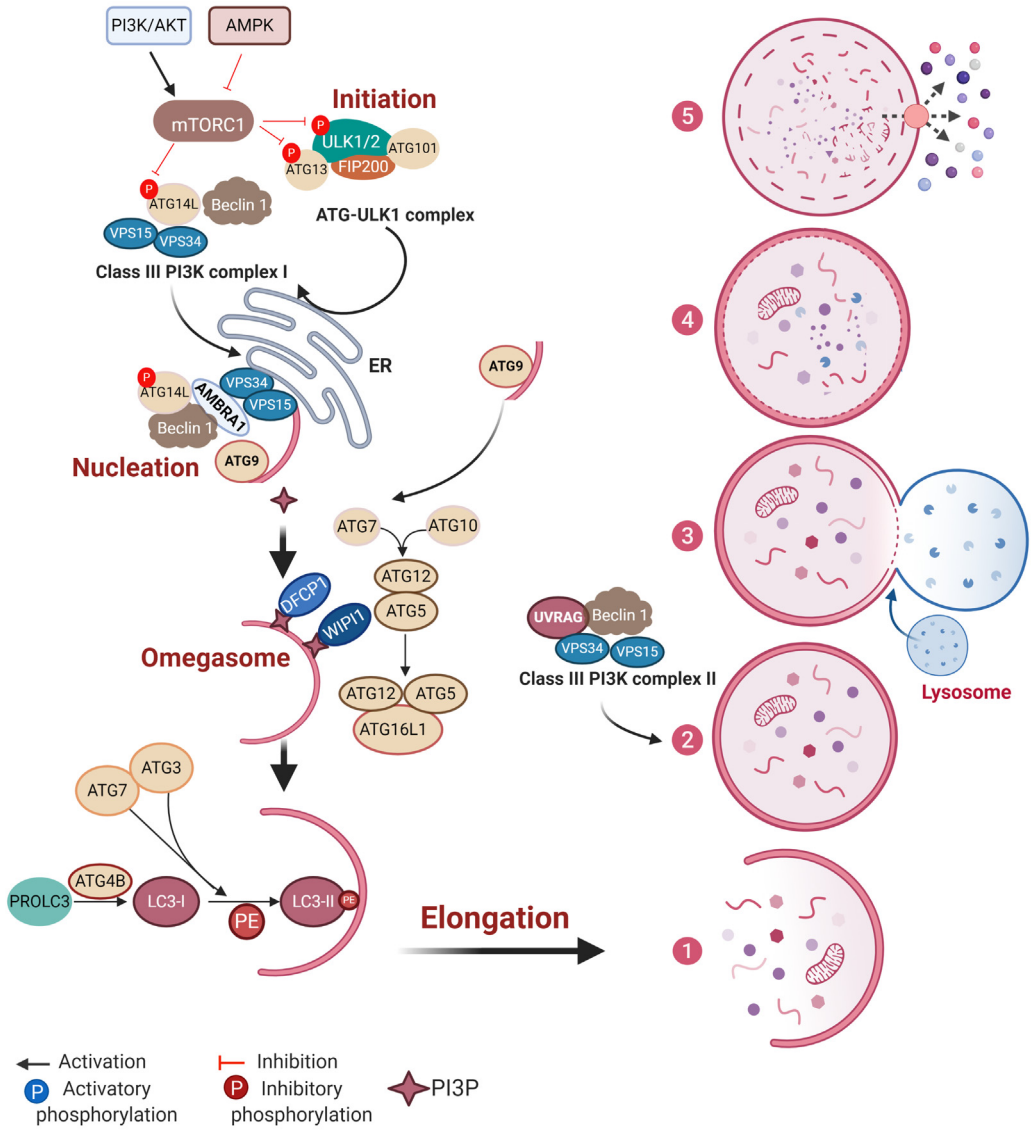

Fig. 2. The autophagy signaling pathway. Activation of autophagy machinery commonly occurs in specific conditions (e.g., nutrient deprivation, infection, or cellular extrinsic stress). Therefore, the autophagic pathway has been engaged in the pathological processes of many age-related diseases. The mTORC1 phosphorylation by Rheb occurs under nutrient-rich conditions, with the consequent inhibition of the autophagy initiators ULK1/2 and ATG13. The ULK1 serine/threonine kinase complex (ULK1, ULK2) acts downstream of the mTOR signaling. ULK1/2 forms a large complex with the scaffold proteins FIP200, ATG101, and ATG13. In mammalian cells, VPS34 forms two heterotetrameric core complexes known as Class III PI3K complexes I and II. Complex I is composed of VPS34, VPS15, Beclin 1, and ATG14L, whereas complex II has UVRAG instead of ATG14L. Whereas the Class III PI3K complex I is required for autophagy initiation, complex II promotes autophagosome maturation and endocytic trafficking. The elongation of the phagophore membrane is driven by two ubiquitin-like conjugation systems: the ATG5-ATG12-ATG16L conjugation system and the LC3-PE conjugation system. Eventually, autophagic vesicles transit towards lysosomes where cargo is degraded (steps 1 to 5). 1: Phagophore formation; 2: Autophagosome formation and maturation; 3: Autophagosome fusion with lysosomes; 4: Autolysosome formation and maturation; and 5: Degradation and recycling of cellular components. Figure created with BioRender.com.

deletions and duplications), single point mutations, gene fusions (e.g., *BCR-ABL*), deletions, and amplifications of genes (e.g., *TP53*, *RB1*, *EGFR*, *BRAF*, and *KRAS*), among others that sustain their metabolic, proliferative behavior, as well as morphological changes (Chakravarthi et al., 2016). Aside from the ability to proliferate uncontrollably, cancer cells must acquire several hallmarks to evolves to a more aggressive stage, including the evasion of regulated mechanisms of cell death (e.g., apoptosis), vasculogenic mimicry capacity, resistance to the antitumor immune response, and the provocation of metastasis (Hanahan and Weinberg, 2011). For instance, melanoma induced by oncogenic B-RAF^{V600E} shows resistance to activation of autophagy through mTORC1-dependent signaling (Armstrong et al., 2011).

Numerous cellular and signaling pathways are engaged during tumor progression, including autophagy. Controversy is raised as to whether autophagy is a tumor-prone process, or whether it is, in fact, a kind of tumor suppressor mechanism (Singh et al., 2018; Grasso et al., 2012). Logic allows us to speculate that the role of autophagy in carcinogenesis depends on the tissue specificity, malignancy state, and the clinical stage. For instance, pro-survival autophagy plays a beneficial role in the setting of a poorly vascularized tumor and resistance to chemotherapy, by preventing intrisinc apoptosis (Huang et al., 2018). Beyond the concept of the degradative pathway, new emerging functions of autophagy have been highlighted in cancer progression, e.g., secretory autophagy, which enables intercellular communication in the tumor microenvironment and may determine the fate of the tumor (Bustos et al., 2020). Besides compromising tumor responses, autophagy also participates in innate and adaptive immune signaling (de Souza et al., 2020). Therefore, it is essential to consider the side effects of autophagy modulation on the

tumor microenvironment and the immune system.

There are still divergent opinions on the appropriate approach to the modulation of autophagy in the clinical context. In summary, accelerating/activating or inhibiting autophagy (in tumor cells) may exert beneficial effects (Fig. 3) and will be discussed below in this review. Several drugs that are licensed for use in humans might regulate autophagy, positively or negatively (Supplemental Tables 1 and 2).

3.1. Autophagy inductors in cancer

The PI3K/AKT/mTOR pathway is one of the most frequently dysregulated signaling pathways in human tumors and is responsible to regulate autophagy, lipid, protein, and nucleotide synthesis, as well as proliferation, and metabolism (Dienstmann et al., 2014). Thereby, once dysregulated, this central signaling pathway might contribute to tumor chemoresistance (Gremke et al., 2020). To deal with this tumor evasion of therapeutic the development of PI3K/mTOR pathway inhibitors has emerged, including specific inhibitors of class I PI3K, AKT as well as of mTORC1 and mTORC2 (Supplemental Table 1) (Fig. 4).

In general, targeting mTORC1 inhibition (e.g., everolimus, temsirolimus, ridaforolimus, and sirolimus/rapamycin) leads to favorable outcomes in various types of cancers (Crazzolara et al., 2009; Pulsipher et al., 2014; Oza et al., 2015; Zibelman et al., 2015; Nemunaitis et al., 2013; Seiler et al., 2015; Armand et al., 2016; Sandmaier et al., 2019; Hess et al., 2015; Hutson et al., 2014; Motzer et al., 2008; Ohtsu et al., 2013; Zhu et al., 2014; Piha-Paul et al., 2015), especially in cases of resistance to chemotherapy (Crazzolara et al., 2009; Seiler et al., 2015; Rangwala et al., 2014a; André et al., 2014; Hurvitz et al., 2015). Disruption of the PI3K/AKT signaling pathway dramatically enhances the efficacy of mTOR inhibitors through hyperactivation of autophagy (Takeuchi et al., 2005), mainly in the case of loss of PTEN (NCT00876395) (Hurvitz et al., 2015). Similarly, the impairment of VSP34 complexes prevents autophagic flux (i.e., autophagosome formation and maturation) and improves the efficacy of everolimus (Ronan et al., 2014; Pasquier, 2015). However, mTORC2-mediated activation of AKT prevents the efficacy of mTORC1 inhibitors, resulting in insufficient 4E-BP1 activation, induction of feedback loops, and occurrence of parallel signaling pathways (Eyre et al., 2014). To overcome tumor resistance, mTORC1/2 or third generation mTORC1 inhibitors (e.g., RapaLink-1) have emerged (Supplemental Table 1). Conversely, clinical findings have shown that dual mTORC1/2 leads to limited efficacy at least for MLN0128 (Graham et al., 2018), AZD2014 (Eyre et al., 2019; Schmid et al., 2019). Though, AZD2014 has demonstrated a favorable safety profile in temozolomide-combined therapy for glioblastoma multiforme at first recurrence (Lapointe et al., 2020).

A recent phase I clinical finding reinforces the activation of autophagy through the AKT/mTOR axis to treat refractory solid tumors (Becher et al., 2017). In fact, allosteric AKT inhibitors may be administered in the case of *PTEN* loss or *PIK3CA* mutations (Davies et al., 2012; Sangai et al., 2012; Hirai et al., 2010). As monotherapy for recurrent glioblastoma, perifosine was less effective, despite being tolerable (Kaley et al., 2019). Nevertheless, its combination with temsirolimus leads to tumor remission regardless of the *PTEN* profile in the murine glioblastoma model (Pitter et al., 2011). In the case of MK-2206, the strategy of co-administration with autophagy inhibitors (e.g., HCQ) does not lead to a favorable clinical efficacy at least against advanced solid tumors (Mehnert et al., 2019). Though, when combined with paclitaxel and carboplatin, MK-2206 triggers enhanced autophagy that upon CQ-combined treatment further increases tumor regression and death of *BRAF*-wild type melanoma cells (Rebecca et al., 2014).

PI3K inhibitors have been considered attractive therapeutic targets (Supplemental Table 1). Even though, tumor cells may experience resistance to the antitumor effects of PI3K modulators (e.g., GDC-0032) due to upregulation of the insulin receptor (IGF1R) (Zorea et al.,

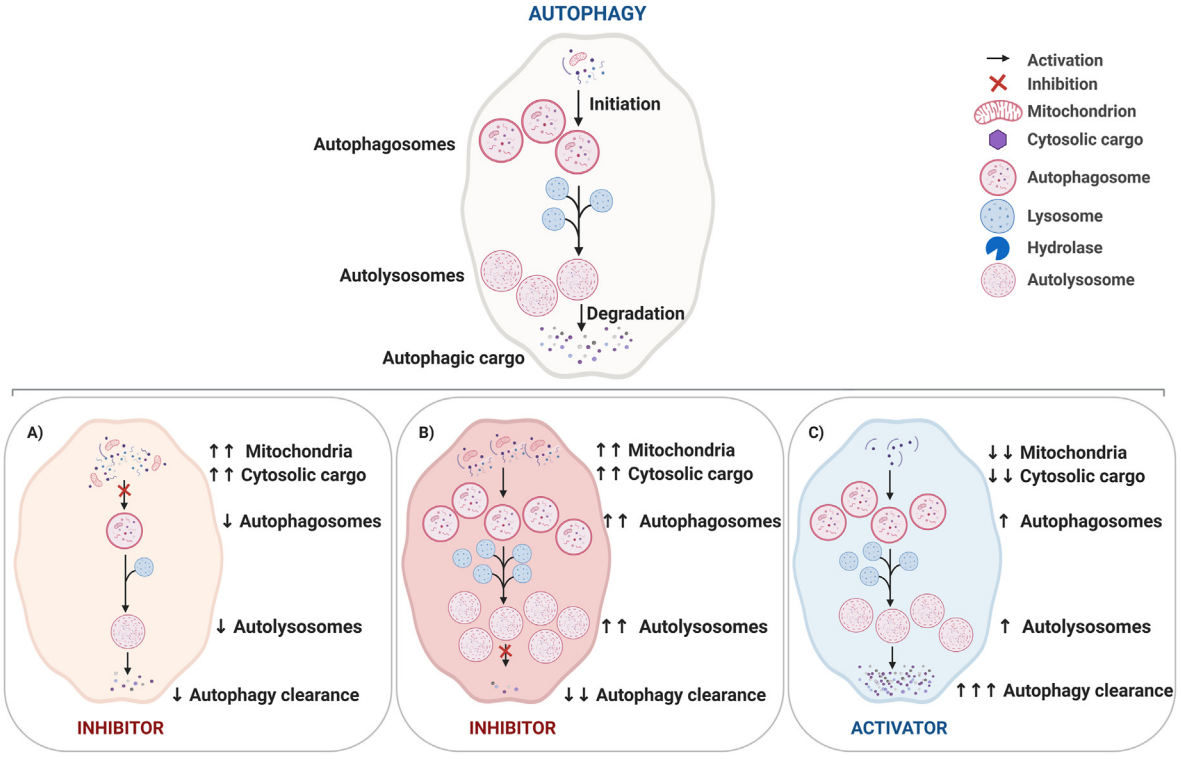

Fig. 3. Principles of autophagy modulation as cancer therapy. Beneficial interventions through modulation of autophagy in cancer cells are commonly associated with inhibition (a and b) or boosting of autophagic flux. Inhibiting autophagy initiation may favor a detrimental accumulation of worn-out mitochondria and less catabolic level (a), whereas jeopardizing lysosomal degradation may support a deleterious and boosted buildup of non-functional autophagosomes and autolysosomes (b), which both effects linked to improved clinical outcomes for cancer. On the other hand, boosting autophagic flux in tumor cells may favor beneficial effects related to the depletion of mitochondria by excessive mitophagy and consequent energy failure. Figure created with BioRender.com.

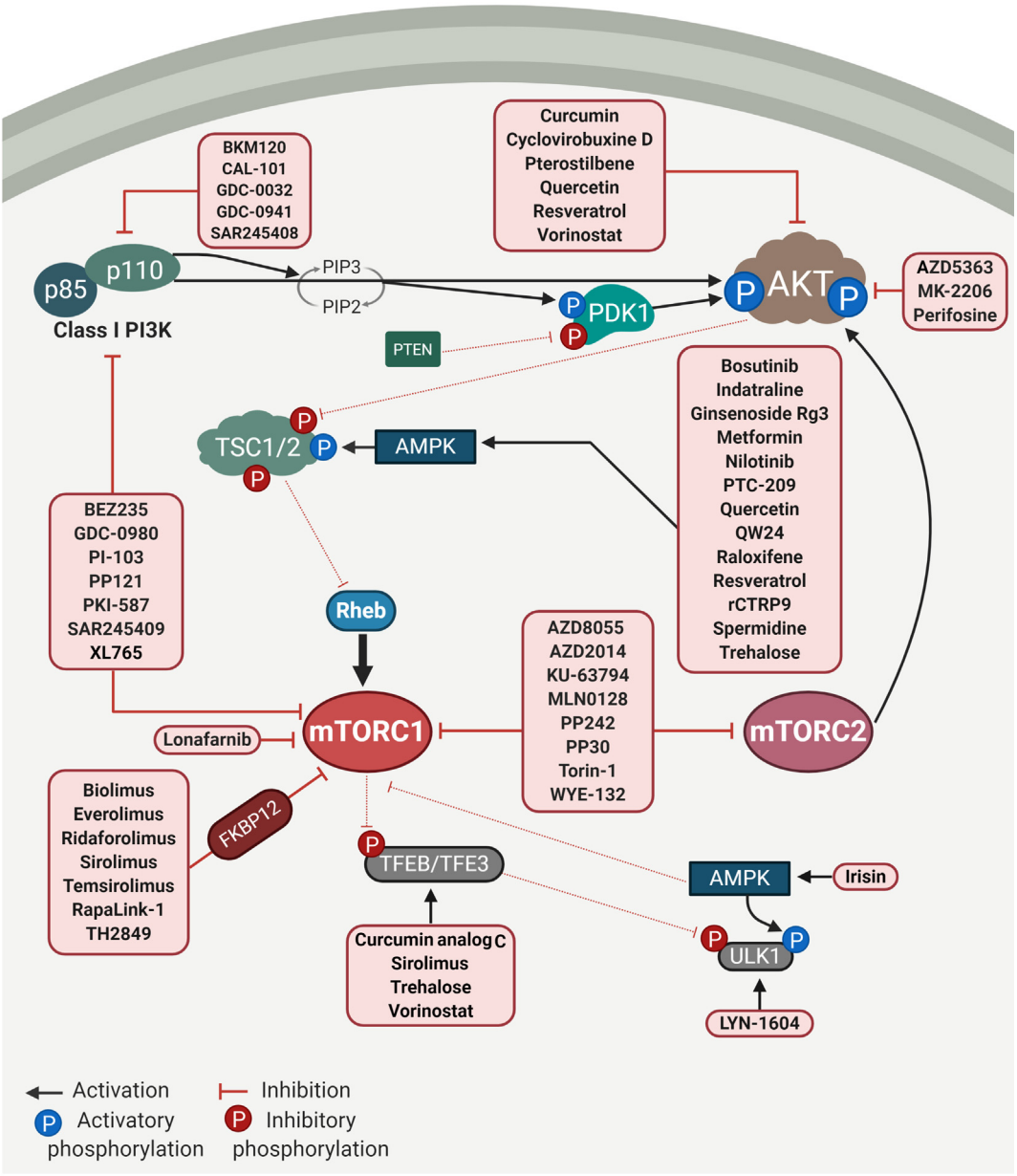

Fig. 4. Overview of the PI3K/AKT/mTOR pathway and drug targets. Drugs that positively (AKT, PI3K, PDK1, and Rheb) or negatively (AMPK, PTEN, TSC1/2 complex) regulate the mTORC1 signaling process are highlighted. Depending on upstream and downstream regulators of these networks' autophagy may be activated or inhibited. Figure created with BioRender.com.

2018). To deal with cancer resistance to PI3K modulators (e.g., CAL-101, SAR245408, BKM120, and GDC-0941), some strategies have emerged: combination therapy with inhibitors, of the proteasome (e.g., bortezomib), of AKT (e.g., MK-2206), of lysosome function (CQ, B10, and bafilomycin A1) and VPS34 (e.g., 3-MA) (Ikeda et al., 2010; Kuo et al., 2014; Zang et al., 2014; Enzenmüller et al., 2013).

As members of the PI3K-related kinases (PIKK) superfamily, both PI3K and mTOR share structural domains, leading to some inhibitory agents targeting them simultaneously (Supplemental Table 1). Thus, downregulation of both upstream (PI3K) and downstream AKT (mTORC1) targets alleviate the negative feedback loop mTORC1–S6K–IRS1 (Dienstmann et al., 2014), even at nanomolar concentrations (Ronan et al., 2014; Apsel et al., 2008; Kenny et al., 2020). Thus, PI3K/mTORC1 inhibitors may increase cancer cell growth inhibition, even in the presence of a *PI3K* mutation (e.g., BEZ235) or chemoresistance (e.g., PKI-587, PI-103) (Serra et al., 2008; D'Amato et al., 2014; Aggarwal et al., 2019; Djuzenova et al., 2019). This effect has been correlated with the long-term activation of autophagy that evokes ATP depletion (Echeverry et al., 2015). In case of tumor relapse to dual PI3K/mTORC1 inhibition (e.g., BEZ235, GDC-0980, PI-103, XL765, or SAR245409) inhibition of lysosome function may be considered (e.g., bafilomycin A1 or CQ) or MEK1/2 (e.g., pimasertib) to enhance tumor remission (Echeverry et al., 2015; Ghadimi et al., 2012; Inaba et al., 2015).

Several other autophagy inductors may be considered for further clinical investigation, mainly those FDA-approved drugs such as metformin (Supplemental Table 1). The antitumor effect of metformin relates to autophagy via the activation of AMPK and a decrease in ATP generation, which improves the *in vitro* results of chemotherapy and photodynamic therapy (Saha et al., 2015; Sesen et al., 2015; Osaki et al., 2017). There are 74 clinical trial entries using metformin as an antitumor agent, mainly against breast, lung, and prostate cancers. To improve the

metformin antitumoral effect, another AMPK modulator has emerged (e.g., nilonitib), the combination of which with HCQ curiously reduces the *in vivo* preclinical efficacy of nilonitib (Yu et al., 2013).

Vorinostat, a histone deacetylase (HDAC) inhibitor, can initiate an ER stress response and activate autophagy by downregulation of AKT/mTORC1, in which the inhibitor 3-MA or knockout of *ATG5* antagonize its cytotoxicity (Liu et al., 2010). Paradoxically, the cytotoxicity of vorinostat increases upon lysosomal inhibition, leading to the accumulation of ubiquitinated proteins in colon cancer cells (Carew et al., 2010). By inducing acetylation of TFEB, vorinostat promotes lysosomal activation, autophagy, and colon cancer cell death (Zhang et al., 2018a). Preclinical suppression of late-stage autophagy flux increases the benefits of vorinostat in brain implanted-mice gliomas (Mayer et al., 2019). Subsequently, the premise of inhibiting autophagy to overcome resistance to vorinostat was corroborated by a phase I clinical trial, in which its co-administration with HCQ reduces tumor relapse (Mahalingam et al., 2014). Its co-administration with a PARP inhibitor olaparib synergistically inhibits tumor cell growth of triple-negative breast cancer cells by increasing apoptosis and autophagy (Min et al., 2015).

MHY218, a new synthetic HDAC inhibitor, induces autophagy and apoptosis in tamoxifen-resistant breast cancer cells (Park et al., 2012). BIX-01294 mediates death by inhibiting euchromatic histone-lysine N-methyltransferase 2 (EHMT2/G9a), leading to ROS-dependent breast cancer cell death *in vitro* (Kim et al., 2013). Recently, BIX-01294 was found to induce death linked to GSDME-mediated pyroptosis and autophagy, and when combined with cisplatin increases gastric cancer cell death (Deng et al., 2020). By inducing the autophagy-lysosome pathway QW24 increases the degradation of BMI1, a protein responsible for the regulation of mitochondrial function (Liu et al., 2009), with the consequent lower proliferative and invasive phenotype of colorectal cancer stem-like cell lines (Wang et al., 2019). Such effect results in tumor suppression of a colorectal cancer xenograft model, as well as less metastasis and extension of mice's lifetime (Wang et al., 2019). The BMI1 inhibitor PTC-209 might up-regulate the AMPK/mTOR signaling and mitophagy, leading to autophagy-mediated necroptosis in ovarian cancer cells (Dey et al., 2016). Besides, PTC-209 was able to decrease the development of glioblastoma with better survival rates than temozolomide chemotherapy (Kong et al., 2018).

Since raloxifene, an estrogen receptor antagonist, detects ATP depletion, it activates autophagy through AMPK-mediated signaling, leading to Beclin 1-dependent death regardless of the induction in breast cancer cells (Kim et al., 2015). The benefit of raloxifene as mono or combination therapy has been studied in a phase I/II clinical trial to prevent or treat several types of cancers.

Several natural products suppress tumor growth by autophagy upregulating (Supplemental Table 1). Curcumin has emerged as an anticancer agent whose combination with HCQ further increases tumor death (Fu et al., 2018). Phase I/II clinical trials have been conducted to evaluate the benefits of curcumin as mono or combination therapy to treat advanced solid tumors (e.g., NCT03072992, NCT04294836, and NCT00094445). Quercetin induces cell death due to inhibition of the PI3K/AKT/mTOR axis after the suppression of *RAGE* expression, which is responsible for increased metastasis and development of drug-resistant pancreatic cancer (Lan et al., 2019).

Another target to enhance autophagy is the class III PI3K/Beclin 1/ATG14 complex 1 that is positively regulated by pterostilbene derivatives (e.g., ANK-199), which specifically triggers cisplatin-resistant oral cancer cell death, *in vitro* and *in vivo* (Hsieh et al., 2014). Recently, the bis(hydroxymethyl)propionate analogs of pterostilbene (C12) highlights as promisor antitumor agents against cisplatin-resistant xenograft nude mouse model (Hsieh et al., 2018), whose beneficial effects may be related to those observed for pterostilbene activation of autophagy through AKT signaling (Chang et al., 2018).

Endoplasmic reticulum stressors are known to positively modulate autophagy. Saikosaponin-d, an inhibitor of the sarcoplasmic/endoplasmic reticulum Ca^{2+}ATPase pump (SERCA), induces intracellular calcium accumulation, which in turn activates the CaMKKβ/AMPK/mTOR cascade signaling, and induces pro-death autophagy in apoptotic-defective tumor cells (Wong et al., 2013).

Using high-throughput *in silico* screening and chemical synthesis, Zhang et al. disclosed LYN-1604 as a new inductor of autophagy-related death by activating the ULK1 complex, whose tumor outcome benefits could be reversed when combined with 3-MA (Zhang et al., 2017). LYN-1604 promoted tumor suppression in breast cancer xenografts related to ULK1 activation (Zhang et al., 2017). The inhibitory effect of the FDA-approved antidepressant imipramine on lysosomal acid sphingomyelinase leads to reduced mTOR phosphorylation and nuclear translocation of TFEB (Justice et al., 2018), resulting in pro-death autophagy in *PTEN*-null human glioma cells (Jeon et al., 2011).

3.2. Autophagy inhibitors in cancer

Over the past decade, undeniable progress has been made in the molecular basis of autophagy that underpins its potential in anticancer therapies. Since blocking the autophagy process by pharmacological or genetic (e.g., knockdown of *Beclin 1*, *ATG,* or *ULK1/2* genes) modulation improves tumor sensitivity chemotherapy (Xiao et al., 2021) or photodynamic therapy (Martins et al., 2021), there has been considerable interest in developing new clinically relevant autophagy inhibitors. For instance, the disruption of up-regulated ATG7 induces tumor cell death by triggering apoptosis, which is strictly dependent on nuclear LC3B (Scherr et al., 2020). On the other hand, with inhibition of VPS34 signal transduction (siRNA therapy), tumor cell proliferation was significantly suppressed after combination chemotherapy (Zhu et al., 2015). Common compounds that have been used to negatively regulate autophagy are listed in Supplemental Table 2. Among them, we highlighted those that compromise the initiation, elongation, maturation of autophagosomes, and their fusion with lysosomes, as well as the autolysosome function (Fig. 5).

The specific targeting of the initial stage of autophagy has become a bona fide drug target for the discovery of anti-cancer treatments, such as inhibitors of i) ULK1/2 (Tang et al., 2017; Egan et al., 2015; Petherick et al., 2015) ii) VPS34 (Ronan et al., 2014; Pasquier, 2015; Dyczynski et al., 2018; Bago et al., 2014), and iii) ATG4B (Chu et al., 2018; Huang et al., 2017; Akin et al., 2014; Fu et al., 2019, 2020; Kurdi et al., 2017). Of note, some of these compounds e.g., SBI-0206965 (Tang et al., 2017; Egan et al., 2015), SB02024 (Dyczynski et al., 2018), UAMC-2526 (Kurdi et al., 2017), or SAR405 (Ronan et al., 2014) synergize with mTOR inhibition e.g., AZD8055 (Egan et al., 2015), everolimus (Ronan et al., 2014), MLN0128 (Egan et al., 2015) or other standard anticancer therapies e.g., sunitinib (Dyczynski et al., 2018), cisplatin (Tang et al., 2017), bortezomib (Ikeda et al., 2010), or oxaliplatin (Kurdi et al., 2017) to promote tumor remission. SAR405 selectively binds and inhibits VPS34, affecting autophagosome formation, maturation, and vesicle trafficking (Ronan et al., 2014). Activation of autophagy by mTORC1/2 inhibitors (e.g., AZD8055 or MLN0128) associated with competitive antagonists of ULK1 (e.g., SBI-0206965) enhances tumor remission (Egan et al., 2015). In the case of pharmacological blockage of ATG4B function (e.g., NSC185058) autophagy impairment and cell death occur regardless of mTOR/PI3K activities (Akin et al., 2014), which reduces the tumorigenicity and may be used to tackle cancer resistance to radiotherapy (Huang et al., 2017). Altogether, these recent advances could pave a way for reliance on autophagy as a druggable cancer target, though further clinical studies are still necessary that consider critical evaluation and validation of these drugs for efficacy, tolerability, and safety. To deal with the safe and tolerability boundaries the repurposing screening of FDA-approved drugs highlights. Based on this premise, targeting autophagy with 60 mg/kg of tioconazole, a known safe antifungal drug, was shown to sensitize tumor xenografts to chemotherapy due to inhibition of ATG4 activity (Liu et al., 2018).

Among all the strategies to negatively modulate the late stage of autophagy flux (Fig. 5), the lysosomotropic agents (e.g., CQ and

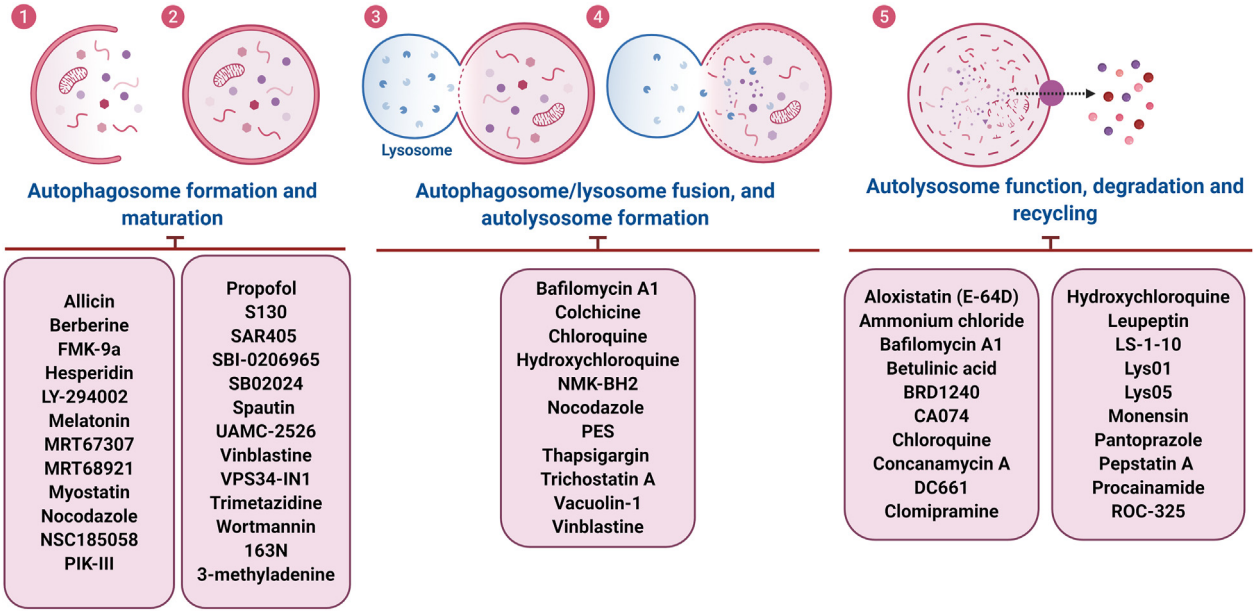

Fig. 5. Autophagy inhibitors and the autophagy pathway. The autophagic machinery can be distinctly divided into 1) initiation, 2) elongation and autophagosome formation, and 3) autophagosome/lysosome fusion, and 4) autolysosome formation, and finally, 5) autophagic degradation and recycling. Many of these steps can be targeted with inhibitory drugs. In the initiation step, mTORC1 can be targeted (see Fig. 2) because it controls the activation of ULK1 and the cascade of events for the formation of the phagophore and degradation of the lysosomal-autophagic system. Figure created with BioRender.com.

derivatives) highlight, since they increase the efficacy of a variety of anticancer agents. CQ and HCQ diffuse across cell membranes and due to their pKa (above 10) they protonate and accumulate inside organelles containing acidic intralumen (pH 4.5), such as endosomes and lysosomes. CQ decreases cancer cell proliferation and synergizes with tyrosine kinase inhibitors (e.g., sunitinib) independently of autophagy (Eng et al., 2016). Furthermore, at least in preclinical trials, adaptive antitumor immunity remains intact after inhibition of autophagy by CQ (Starobinets et al., 2016). It can also function as an anti-tumor immunomodulator through a macrophage-based modality (Starobinets et al., 2016). Towards this end, CQ resets altered macrophages from the tumor microenvironment due to a decrease in immunosuppressive infiltration settings (e.g., myeloid-derived suppressor cells and Treg cells), and thus, enhanced immunity of antitumor T-cell (Chen et al., 2018a). However, treatment with the autophagy inhibitor HCQ reduced T cell-mediated tumor killing, supporting the importance of further delineating how autophagy regulates tumor-specific immune response (Peng et al., 2016). Although monotherapy achieved low therapeutic efficacy (Wolpin et al., 2014), CQ or HCQ based therapy combined with other interventional approaches has improved clinical outcomes for several human cancers (Mahalingam et al., 2014; Zeh et al., 2020; Boone et al., 2015; Sotelo et al., 2006; Briceño et al., 2003; Rojas-Puentes et al., 2013; Vogl et al., 2014; Rangwala et al., 2014b, 2014c; Goldberg et al., 2012). Even though these beneficial effects highlighted HCQ as an "*old repurposing drug*" in oncology, they restrict pharmacology and toxic retinopathy (Amaravadi et al., 2019; Abdulaziz et al., 2018). Thus, a definitive approach that relies on autophagy as an adjuvant cancer therapy should contemplate the development of lower-toxicity agents that can perform more efficient inhibition of autophagy than HCQ (Rosenfeld et al., 2014; Karasic et al., 2019). In consequence, several other lysosomotropic drugs have been investigated (Lys01, Lys05, LS-1-10, and ROC-325), establishing their therapeutic potential to treat cancer in humans (McAfee et al., 2012; Carew et al., 2017; Nawrocki et al., 2019).

There is an increasing awareness that weak-base amphiphilic drugs (e.g., HCQ) due to their intrinsic basicity have inconsistent cellular penetration into the acidic tumor microenvironment (Pellegrini et al., 2014). Efforts are underway to address this issue. For instance, dimeric chloroquine (DC661) has higher cell diffusion and lysosomal localization in the acidic tumor microenvironment (Rebecca et al., 2019). Besides, DC661 binds to and inhibits the activity of PPT1 (Palmitoyl-protein thioesterase 1), a protein that is associated with poor survival in patients with a variety of cancers. PPT1 plays an important role in stabilizing the lysosomal localization of V-ATPase subunits, which provides: 1) maintenance of the lysosomal acidity necessary for proficient autophagy, and 2) facilitate the critical machinery for mTOR localization and subsequent activation. Aside from DC661, HCQ and Lys05 can also inhibit PPT1 (Rebecca et al., 2019).

Pentacyclic triterpenoid betulinic acid and its derivatives have been considered an alternative mechanism to compromise autophagy based on disturbance of the organelle membrane (Martins et al., 2015, 2017; Gonzalez et al., 2012), resulting in a mitochondrial-lysosomal axis of cellular stress that causes autophagy associated cell death and aging (Martins et al., 2015, 2017). This modulation of autophagy for organelle-targeting therapy represents a promising avenue to induce tumor regression (Martins et al., 2016, 2019; Tsubone et al., 2020). Some mechanisms of tumor resistance to drugs are mediated by lysosome; as is the case with the lysosomal sequestration of multiple weak-base hydrophobic drugs, including tyrosine kinase inhibitors (e.g., sunitinib) (Gotink et al., 2011). Such organelle-mediated drug sequestration keeps these drugs away from their intracellular sites, hence resulting in tumor resistance (Wu et al., 2020). The approved drug pantoprazole used for the management of gastroesophageal reflux disease significantly increases the sensitivity of tumor xenografts to paclitaxel by inhibiting autophagy (Tan et al., 2017). Besides, the cytotoxicity of pantoprazole is synergically enhanced when combined with BCL-2 inhibitors (e.g., ABT263 and ABT737), increasing mitochondrial dysfunction and apoptotic death of tumor cells (Cao et al., 2018). Moreover, ammonium chloride (Ikeda et al., 2013), bafilomycin A1 (Wu et al., 2020; Wiedmer et al., 2017), concanamycin A (Ellegaard et al., 2013), CQ (Wu et al., 2020; Wiedmer et al., 2017; Li et al., 2018a), Lys05 (DeVorkin et al., 2017), or SB02024 (Dyczynski et al., 2018) improve cancer sensitivity to sunitinib, being a promising therapeutic target when tumor resistance to drugs is mediated by the lysosomal-trapping.

Colchicine has been considered an attractive drug for sensitizing tumor cells to death through impairment of the autophagic flux (Bhattacharya et al., 2016), probably by blocking of autophagosome

maturation to autolysosomes (Ju et al., 2010). The phase II clinical trial NCT04264260 aims to investigate its potential palliative effects against liver cancer. Vinblastine (Xie et al., 2010; Köchl et al., 2006) and nocodazole (Xie et al., 2010) also may improve tumor response to chemotherapy, by disrupting the late stage of pro-survival autophagy. Consequently, current or completed phase II/III trials investigated the benefits of combining vinblastine with standard chemotherapies, such as methotrexate, cisplatin, or doxorubicin.

The approved anesthetic drug propofol (Diprivan®) was shown to block autophagosome-lysosome fusion, in addition to inducing endoplasmic reticulum stress (Chen et al., 2018b). Moreover, its late effect decreases the pro-survival autophagy triggered by chemo-resistant cells and enhances the antitumoral efficacy of cisplatin through the lncRNA MALAT1/miR-30e/ATG5 pathway (Zhang et al., 2020a). Accordingly, due to these anticancer effects, some clinical trials have been conducted concerning the impact of propofol on tumor prognosis or cancer immunity (Gao et al., 2020).

4. Use of autophagy modulators for neurogenerative disorders

Neurons are highly specialized postmitotic cells, which depend on dynamic cellular processes, including neuronal growth and maturation, axonal migration, synapse formation, and elimination, for their proper functions (Nikoletopoulou et al., 2015). All these processes require the maintenance of balanced protein synthesis and degradation (i.e., proteostasis). Unlike mitotic cells, neurons do not rely on cell division to dilute their intracellular excess burdens. In this context, the proper function of the autophagy pathway is crucial to prevent the accumulation of dysfunctional organelles and waste over a lifetime (Hussain et al., 2018). Therefore, neuronal physiology is especially vulnerable to impairment in the removal of autolysosomal-sequestered substrates, which is related to cancer, neurodegeneration, and inflammatory disease (Hussain et al., 2018). Accumulation of protein aggregates is a hallmark for many adult-onset neurodegenerative diseases, e.g., Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and spinocerebellar ataxia (SCA) (Rubinsztein et al., 2015).

Mouse models with disruption of autophagy genes, such as ATG5, ATG7, FIP200, or ULK1/2, develop early signs of neurodegeneration with an intraneuronal accumulation of ubiquitinated protein aggregates regardless of the presence of disease-causing mutations, suggesting that disabled autophagy process or flux contributes to the etiology of neurodegenerative diseases (Komatsu et al., 2006; Hara et al., 2006). In AD, the abnormal cleavage of the amyloid precursor protein (APP) results in the accumulation of amyloid-β (Aβ) and the formation of extracellular Aβ plaques (Suresh et al., 2018). Also, intracellular tangles of hyperphosphorylated tau protein are observed (Suresh et al., 2018). Protein aggregates can be specifically removed by autophagy and, in fact, Aβ is reduced with upregulation of autophagy (Suresh et al., 2018). Recently, the loss of PICALM (phosphatidylinositol/binding clathrin protein) function was described in AD (Ando et al., 2016). PICALM is a protein-related to vesicular trafficking and its loss has negative effects on several steps of the autophagy flux. Besides, it is suggested that PICALM is an adaptor protein between Aβ and LC3 (Moreau et al., 2014; Tian et al., 2013).

Of the neurodegenerative diseases, PD is the most linked to autophagy failure. The impaired motor control and cognitive decline observed in PD are due to the progressive elimination of dopaminergic neurons located in the substantia nigra. The hallmark of those neurons is the presence of α-synuclein protein aggregates. Some types of early-onset hereditary PD are associated with gene mutations that affect PINK and/or Parkin proteins which are keys for selective autophagy-mediated elimination of damaged mitochondria (mitophagy) (Barazzuol et al., 2020). Other causative genes of PD are also related to autophagy as is the case of the vesicular trafficking protein VPS35 whose mutation impairs the normal behavior of ATG9 (Zavodszky et al., 2014). In HD, the repeat expansion of polyglutamine-encoding CAG codon leads to an anomalous huntingtin protein (muHTT). Data support that HTT functions as a scaffold protein for selective autophagy of mitochondria and protein aggregates (Gelman et al., 2015). Then, muHHT interferes with autophagosome selective cargo recognition. Besides, the sequestration of the key autophagy protein Beclin 1 into protein aggregates was observed in HD experimental models (Ashkenazi et al., 2017). ALS and FTD represent motor and cognitive neurodegenerative diseases, respectively. Today, ALS and FTD are considered a continuum since they share many pathological and genetic features (Abramzon et al., 2020). Beyond the superoxide dismutase 1 (*SOD1*), the first gene associated with ALS, ALS, and FTD share many cause-related genes such as *C9ORF72*, fused in sarcoma/translocated in sarcoma (*FUS*) and TDP-43, among many others. TDP-43-positive cytoplasmic aggregates are present in 97% of ALS cases, followed by those where SOD1 or FUS are the preponderant aggregated proteins. FTD can also be subclassified by the major protein associated with the glial and neuronal inclusions, that is the case for tau (FTLD-tau), TDP-43 (FTLD-TDP), or FUS (FTLD-FUS) (Abramzon et al., 2020). Interestingly, most of those genes are somehow associated directly or indirectly with different aspects of the autophagy pathway. Mutation in C9ORF72 is the most common cause of familial ALS/FTD and it is of importance to autophagy since C9ORF72 regulates endosomal trafficking (Aoki et al., 2017). Moreover, C9ORF72 interacts with ULK1 and plays a role in its recruitment to the isolation membrane during autophagosome biogenesis (Webster et al., 2016).

As intraneuronal aggregates and impairment of autophagy are characteristics of most adult-onset neurodegenerative diseases, efforts are focused on strategies to enhance autophagy response. The first logical approach is the inhibition of mTOR signaling that negatively regulates autophagy. The specific mTORC1 inhibitor, rapamycin, and its derivatives (rapalogs) demonstrated to alleviate neuropathology and neurodegeneration in several transgenic models of pathogenic proteins, including models of HD (mutant HTT) (Ravikumar et al., 2004; Sarkar and Rubinsztein, 2008), AD (mutant APP) (Spilman et al., 2010; Caccamo et al., 2010), SCA type 3 (Menzies et al., 2010), and PD (mutant α-synuclein) (Webb et al., 2003). Rapamycin decreases neuronal death in MPTP-mediated PD animal models (Ding et al., 2019; Liu et al., 2013a). Furthermore, rapamycin diminishes muHTT fragments toxicity in cellular and mice models (Ravikumar et al., 2004). In AD, rapamycin and temsirolimus increase autophagy-mediated elimination of hyperphosphorylated tau with the consequent cognitive improvements in transgenic mice of mutated tau protein (Jiang et al., 2014; Ozcelik et al., 2013). In another mouse model with the expression of a mutated APP, long-term rapamycin treatment decreases Aβ levels and alleviates the AD phenotype (Spilman et al., 2010). Likewise, beneficial effects over neurodegeneration are observed with new rapalog compounds such as TH2849 which is an FKBP12-FK506 derivative (Ding et al., 2019). Despite the promissory results of rapamycin and rapalogs, they cannot be generalized to all neurodegenerative diseases since mixed data are obtained for ALS. In transgenic mouse and *Drosophila* models of TDP-43 proteinopathy, rapamycin was beneficial and able to rescue motor dysfunction (Cheng et al., 2015; Wang et al., 2012). However, in stark contrast, rapamycin accelerated the ALS phenotype onset and shortened the lifespan of the $SOD1^{G93A}$ transgenic mouse (Zhang et al., 2011a). Recently, the mTORC1/2 inhibitors OSI-027, AZD2014, and AZD8055 showed better efficacy than rapamycin on tau clearance in an *ex vivo* human model of tauopathy (Silva et al., 2020). However, the clinical efficacy of OSI-027 and AZD8055 might be limited due to poor brain permeability since transporters at the blood-brain barrier promoted their efflux (e.g., Pgp/ABCB1, BCRP). Silva et al. showed brain penetration of AZD2014 resulting in free brain concentrations at tolerated doses for humans (Silva et al., 2020). Altogether, rapamycin and rapalogs are promising candidates to mitigate misfolded protein aggregates that cause neuronal toxicity, though there is still a long way to go.

The so-called mTOR-independent autophagy inductors can induce autophagy without the side effects related to mTORC1 inhibition. Most of

those molecules rely on activating the AMPK pathway to induce autophagy. Metformin and nilotinib are AMPK modulators that demonstrated neuroprotective qualities in animal models and humans (Patil et al., 2014; Karim et al., 2020). The same two drugs and bosutinib, another AMPK modulator, show phenotype improvements in genetically modified mice for amyloidogenic APP processing that resembles AD (Lonskaya et al., 2014, 2015). Plant-based polyphenols, such as resveratrol, also activate AMPK and show neuroprotective benefits in experimental models of neurodegenerative diseases, particularly in AD (Vingtdeux et al., 2010). A phase II clinical trial points out resveratrol as a promising modulator of adaptive immune response that may improve brain outcome to Aβ deposition (Moussa et al., 2017). Similar results are observed in PD, where resveratrol protected dopaminergic neurons in PD models induced by MPTP (Blanchet et al., 2008) or 6-OHDA (Khan et al., 2010). In ALS, opposite to results of rapamycin-mediated autophagy induction, resveratrol treatment ameliorates disease phenotype and extends the lifespan of $SOD1^{G93A}$ mouse (Han et al., 2012; Mancuso et al., 2014). Besides, the flavonols kaempferol and kaempferide induced AMPK-mediated autophagy, decreased SOD1 aggregation, and prevented neurotoxicity in a $SOD1^{G85R}$ cellular model (Ueda et al., 2017). Quercetin, which is another natural polyphenol from many fruits and vegetables, protects against cholesterol-induced neurotoxicity through AMPK-mediated autophagy (Lu et al., 2010). Recently, a systematic review about preclinical studies highlighted the efficacy of quercetin to alleviate AD since it inhibits Aβ aggregation and tauopathy as well as ameliorates mitochondrial dysfunction (Zhang et al., 2020b).

The disaccharide trehalose induces autophagy, probably through AMPK activation, and enhances clearance of muHTT, α-synuclein, and tau while conferring neuroprotective effects (Sarkar et al., 2007; Casarejos et al., 2011; Rodríguez-Navarro et al., 2010). Additionally, trehalose downregulates AKT activation leading to enhanced activity of TFEB, which is the major transcription factor of the autophagy/lysosomal pathway (Rusmini et al., 2019). Trehalose alleviates neuroinflammation and motor deficit in animal PD models (Pupyshev et al., 2019; Khalifeh et al., 2019; Howson et al., 2019) and decreases the pathologic phenotype in a HD mouse model with muHTT (Tanaka et al., 2004). In mouse models of ALS ($SOD1^{G93A}$ and $SOD1^{G86R}$), trehalose treatment delays phenotype onset and promotes neuronal survival, though the effects are only present in the early steps of the disease (Li et al., 2015; Castillo et al., 2013).

Rilmenidine and clonidine, two FDA–approved antihypertensive agents that bind to imidazoline receptors, provoke clearance of α-synuclein and reduction of HTT aggregation through the autophagy regulation in a mTOR-independent manner (Williams et al., 2008). Phase II clinical trials have been conducted to study the clonidine efficacy and safety to treat PD (e.g., NCT03552068 and NCT01370811). In a zebrafish model, these antihypertensive drugs enhance the clearance of tau, helping to ameliorate the neurodegenerative phenotype (Lopez et al., 2017). In the $SOD1^{G93A}$ mouse, rilmenidine induced autophagy in spinal cords and motor neurons but at the same time, it worsened the ALS neurodegenerative phenotype causing the accumulation of SOD1 inclusions (Perera et al., 2018). In that work, the authors also found that rilmenidine induces severe mitochondria removal suggesting that its deleterious effects could be driven by excessive mitophagy (Perera et al., 2018). Felodipine and verapamil, which are L-type calcium channel blockers used as antihypertensive drugs, demonstrated the capability to induce AMPK-mediated autophagy and generate neuroprotection against diverse aggregate-prone proteins (Zhang et al., 2019a; Popović et al., 2020; Siddiqi et al., 2019). For instance, verapamil induced the autophagy flux, decreased SOD1 aggregates, and prolonged the lifespan of $SOD1^{G93A}$ mice (Zhang et al., 2019a). At low concentrations, felodipine induces autophagy and shows protective effects in a zebrafish model of HD and a mouse model of PD (Siddiqi et al., 2019).

Lithium, which is used as a mood-stabilizing drug, induces autophagy regardless of the mTOR pathway. On the one hand, lithium impairs the inositol monophosphatase signaling that leads to AMPK activation (Sarkar et al., 2005; Motoi et al., 2014), on the other, it inhibits GSK3β allowing a transcriptional induction of autophagy-mediated by TFEB (Mendes et al., 2009). Lithium enhances the cellular removal of toxic autophagic substrates, including aggregate-prone forms of HTT and α-synuclein (Rybakowski J, 2016; Serafini et al., 2016; Kim et al., 2011b). According to a phase I trial (NCT04273932), lithium might alleviate PD by modifying the neurodegenerative effects. Furthermore, in AD, lithium reduced tau phosphorylation in a murine model (Zhang et al., 2011b) and demonstrated neuroprotective qualities in a trial with AD patients (Forlenza et al., 2019). Nevertheless, in several other short-term AD clinical trials, lithium demonstrated negative results in AD patients with mild cognitive impairments (Forlenza et al., 2012). Some reports affirm autophagy-dependent neuroprotection *in vivo* and *in vitro* models of ALS after lithium administration (Feng et al., 2008; Yin et al., 2019). A pilot clinical study with lithium as an autophagy inducer showed a delay in ALS progression (Fornai et al., 2008). However, a recompilation of subsequent clinical trials concluded the lack of statistically significant benefits of lithium administration on ALS patients (Gamez et al., 2016).

An alternative approach to target the autophagy pathway in neurodegenerative diseases is to promote the autophagy/lysosomal function, through the transcription factor TFEB. This must be carefully evaluated for AD because TFEB appears to have a double effect on the Aβ generation. In primary cultures under basal conditions, TFEB post-transcriptionally increases the secretase ADAM10 preventing amyloidogenic processing of APP, but with excess levels of APP or β-CTF, overexpression of TFEB leads to increase Aβ production, probably by interfering with the proteasomal system (Yamamoto et al., 2019). However, the small molecule termed curcumin analog C1 binds and activates TFEB *in vitro* and *in vivo* independently of mTOR inhibition, resulting in increased autophagy and lysosomal activity, and reduction in APP, β-CTF, Aβ, and tau aggregates (Song et al., 2016, 2020).

ADAM30 is also associated with Aβ production, as it is necessary for cathepsin D activation and the subsequent degradation of APP in lysosomes. Moreover, ADAM30 expression is inversely correlated with Aβ levels in AD brains (Letronne et al., 2016). In this direction, the non-peptidic compound PADK (Z-Phe-Ala-diazomethylketone) enhances lysosomal cathepsins, ameliorates the autophagy/lysosomal pathway, and protects against the accumulation of AD-type protein in neurons (Viswanathan et al., 2012). Derivatives SD1002, SD1003, and SD1006 produce more cathepsin up-regulation than PADK, and SD1002 protects against synaptic compromise in a transgenic model of AD by enhancing the active form of cathepsin B and clearance of Aβ (Viswanathan et al., 2012). Lonafarnib (also known as SCH66336), which also increases the lysosomal/autophagy pathway, has been considered a promising candidate for tauopathies treatment (e.g., AD and HD) (Hernandez et al., 2019). Besides, lonafarnib attenuates Rhes-mediated tau accumulation due to the inhibition of farnesyltransferase responsible for the prenylation of Rhes, a small guanosine triphosphatase (GTPase) member, which modulates the aggregation state of muHTT in HD (Hernandez et al., 2019). By the side of ALS, the non-selective inhibitor of phosphodiesterases and anti-inflammatory drug ibudilast inhibits mTORC1 and enhances TFEB nuclear translocation, which in turn increases the clearance of TDP-43 and SOD1 aggregates in cellular models (Chen et al., 2020a). Interestingly, rapamycin and some rapalogs were found to activate autophagy independently of the mTOR lessening through a mucolipin 1-TFEB pathway. In lysosomal membranes, rapalogs bind directly and activate the ion channel receptor mucolipin 1 which in turn promotes a substantial release of lysosomal Ca^{2+} leading to TFEB activation (Zhang et al., 2019b). Furthermore, since the lysosomal associated membrane protein 2 A (LAMP2A) function decline with age (Xilouri and Stefanis, 2016), it has been suggested that targeting LAMP2A induces or enhances chaperone-mediated autophagy (CMA) might be used in neurodegenerative disorders (Xilouri and Stefanis, 2015). Overexpression of LAMP2A or HSC70 (protein associated with CMA) increases the clearance of muHTT protein (Qi et al., 2012). On the contrary,

Yang and Tohda proposed that the functional inhibitor of HSC70 VER-155008 may alleviate memory deficit and axonal degeneration in an animal model of AD (Yang and Tohda, 2018).

Beyond the approaches mentioned above, other strategies are being explored. In neurodegenerative diseases, there is abnormal and sustained activation of the PI3K/AKT/mTOR axis (Xu et al., 2020) and PI-103, dual PI3K/mTOR inhibitor, protected against pathological aggregates of α-synuclein, a hallmark of PD (Höllerhage et al., 2019). Others compounds include PP2A agonists, which inhibit tau hyperphosphorylation, promote autophagy through the mTORC1 and AMPK pathways, and are currently in clinical trials for AD (Magnaudeix et al., 2013). Another experimental approach is to directly induce the autophagy machinery using a viral therapeutic agent to target the Beclin 1/Class III PI3K complex. Intracerebral virus-mediated overexpression of Beclin 1 increases the clearance of aggregation-prone proteins and delays the disease on-set in transgenic mouse models of PD and SCA type 3 (Nascimento-Ferreira et al., 2011; Spencer et al., 2009). Histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid, may also have neuroprotective effects in HD models (Hockly et al., 2003) since the acetylation of muHTT protein specifically targets it to autophagosomes (Jeong et al., 2009). Finally, the recently described autophagy-flux inductor molecule named AUTEN-67 (autophagy enhancer 67) reduces APP levels in a mouse model of AD (Papp et al., 2016) and prevents the progression of HD symptoms in a drosophila model (Billesa et al., 2016).

Summarizing data, many aggregation-prone proteins (e.g., Aβ, muHHT, APP, β-CTF, or tau) with a tendency to aggregate are highly dependent on the autophagy machinery for their removal in a process that seems to be central to the pathogenesis of many adult-onset neurodegenerative diseases (Menzies et al., 2015). So far, there are no successful therapeutic strategies capable of reversing or preventing autophagy-related neurodegeneration in humans. Given the diverse physiological roles of AMPK/mTOR signaling cascades, the dramatic off-target effects could serve as a caveat when designing a possible therapeutic approach. For instance, despite lithium and rilmenidine activate autophagy in the mutant $SOD1^{G93A}$ mouse, they do not slow disease progression (Perera et al., 2018; Pizzasegola et al., 2009). On the other hand, rilmenidine showed promising effects against HD in a transgenic mouse model (Rose et al., 2010) and humans (Underwood et al., 2017), as it also has a neuroprotective function (Mercer et al., 2017). These mixed results could be due to the specific role autophagy plays in each disease. So we need a deeper understanding of the pathogenic mechanisms to build a holistic view of the problem. As an example, most genes that cause ALS/FTD belong to two defined and unrelated pathways: RNA metabolism (e.g., TDP-43 and FUS) and protein quality control (e.g., C9ORF72, VCP/p97, SQSTM1/p62, and optineurin). Recently demonstrated, stress granules, which are ribonucleoprotein granules dedicated to RNA processing composed of RNA-binding proteins, are in fact removed by a selective type of autophagy. Accordingly, in ALS/FTD diseases, the aggregates could be caused by overwhelmed autophagy (Monahan et al., 2016; Mandrioli et al., 2020). Furthermore, very interesting recent data show how exosomes, which are highly associated with the autophagy pathway, spread neurodegenerative diseases by transporting material from disease cells that are capable of promoting protein misfolding to target cells (Vassileff et al., 2020).

The significance of autophagy induction during neurodegenerative disease development is not straightforward. Ongoing studies suggest that in the early stages of the disease, the induction of autophagy could be compensatory and neuroprotective in response to mutant or damaged proteins and aggregates, which in the presence of compromised lysosomal clearance in late stages, may become counterproductive (Nixon, 2013; Bar-Yosef et al., 2019). Thus, unbalanced autophagy induction or defects to complete degradation may further aggravate the pathology (Nixon, 2013; Bar-Yosef et al., 2019; Colacurcio et al., 2018). Finally, the success of an intervention based on autophagy probably depends on alleviating the specific block in the lysosomal clearance process, consequently, greater understanding is necessary to establish a safe and efficient therapeutic outcome for each neurodegenerative disease.

5. Use of autophagy modulators in the treatment of cardiovascular diseases

Virtually all cell types that constitute the cardiovascular system (e.g., cardiomyocytes, endothelial cells, and arterial smooth muscle cells) rely on autophagic machinery for their homeostasis and physiological functions (Bravo-San Pedro et al., 2017). Hence, autophagy plays a pivotal role in the maintenance of heart function and vascular homeostasis, besides it is highlighted also in the pathogenesis of several cardiovascular diseases (CVD) (Global Health Estimates Technical Paper WHO/HIS/IER/GHE/2018.3, 2018). However, the dynamic of autophagy flux seems to differ in each of the CVD types, whose pathogenesis may be intrinsically associated with distinct autophagic signals (protective or deleterious effect) (Gatica et al., 2015).

Regulation of cardiac tissue homeostasis is influenced by the mTOR pathway (North and Sinclair, 2012), and preclinical studies suggest the use of mTORC1 inhibitor rapamycin to improve cardiac function and regress cardiac hypertrophy (i.e., the increased cell size of myocyte) under pressure overload (i.e., ascending aortic constriction) (Shioi et al., 2003; McMullen et al., 2004a). Macrophages destabilize atherosclerotic plaque formation, causing acute coronary syndromes and unexpected death (Martinet et al., 2007). However, atherosclerosis treatment might be followed by restenosis, which is commonly a recurrence that requires repeat angioplasty, bypass surgery, or intravascular radiation. Some clinical studies have investigated the efficacy of rapamycin and rapalogs in reducing or preventing restenosis, probably due to their inhibitory effects on smooth muscle cell growth (Sousa et al., 2003). Thereby, the protective role of autophagy remains a topic of investigation through pharmacological intervention using mTOR inhibitors (e.g., everolimus), which might selectively remove macrophages from atherosclerotic plaques without altering smooth muscle cells (Verheye et al., 2007; Martinet et al., 2014). Besides, autophagy induction can prevent cardiac remodeling and hypertrophy after myocardial infarction (Buss et al., 2010). The antidepressant drug indatraline promotes cell growth inhibition of smooth muscle cells, inhibition of neointimal hyperplasia, and thus relieves restenosis in rats (Cho et al., 2016). Whereas indatraline targets autophagy via the AMPK/mTOR pathway (Cho et al., 2016), rapalog biolimus inhibits mTORC1 signaling leading to mitigation of restenosis-mediated autophagy (Kim et al., 2018). Recently, the third generation of mTORC1 inhibitor, RapaLink-1, showed superior effects on the mTOR pathway, resulting in activation of autophagy and protection from thrombosis-related diseases including atherosclerosis, antiphospholipid syndrome (APS), and stroke (Mu et al., 2020). RapaLink-1 potentially suppresses thrombus plaque formation in antiphospholipid syndrome, with a decrease in the extent of macrophage infiltration and activation of the autophagy process both *in vitro* and *in vivo* (Mu et al., 2020).

Instead of mTORC1, the participation of mTORC2 in cardiac aging remains unclear, however, a recent study has emerged a novel regulation of autophagy in the drosophila model of cardiac aging, showing crosstalk between TGFBINHB/activin and mTORC2 (Chang et al., 2020). A previous study demonstrated that TGFB signaling plays an important role in several diseases (Akhurst and Hata, 2012), being its INHB/activin member an emerging target for the treatment of age-related cardiovascular disease due to its regulatory role in mTORC2 function (Chang et al., 2020).

Altogether, rapalogs or regulators of AMPK/mTOR signaling have been highlighted as an attractive and favorable avenue to treat or prevent infarct-onset, cardiac dysfunction, or atherosclerosis. Metformin activates PINK1-AMPK mitophagy and ameliorates cardiomyopathy, decreasing fibrosis and cardiomyocyte hypertrophy and degeneration in hearts of δ-Sarcoglycan-deficient mice (Kanamori et al., 2019). Besides, this drug might alleviate diabetic cardiomyopathy by upregulating AMPK-autophagy in OVE26 mice, an established model of type 1

diabetes (Xie et al., 2011). However, most of the findings are based on preclinical studies and are still the subject of investigation in clinics.

There is a consensus in cardiac hypertrophy that autophagy is a complex process controlled by several stimuli beyond the PI3K/AKT/mTOR pathways as reviewed (Shimizu and Minamino, 2016), which is linked to IGF1R overexpression in a PI3K (p110α)-dependent manner and autophagy inhibition (McMullen et al., 2004b). In the case of myocardial ischemia, Rheb has been considered a critical negative regulator of autophagy (Sciarretta et al., 2012). Re-expression of *ATG7* and inhibition of mTORC1 lead to an increased cellular ATP content and reduction of ER stress, with consequent reduction of Rheb-mediated cardiomyocyte death (Sciarretta et al., 2012).

By enhancing autophagic flux, the natural polyamine spermidine extends the lifespan of mice due to its cardioprotective effect in old mice, including the reduction of heart hypertrophy and preservation of diastolic function (Eisenberg et al., 2016). In humans, high levels of spermidine obtained from the diet control blood pressure and decrease CVD incidence (Eisenberg et al., 2016). Even though the mechanistic details were hitherto unclear, the properties of spermidine are primarily due to its ability to modulate autophagy, which might preserve the function and structure of cardiomyocytes (Eisenberg et al., 2016). In cardiac dysfunction caused by myocardial infarction, spermidine protects by inducing autophagy through upregulation of the AMPK pathway (Yan et al., 2019). Irisin attenuates pressure overload-induced cardiac hypertrophy mediated by angiotensin II (Ang II) or phenylephrine (PE) through activation of protective autophagy via AMPK-ULK1 activation regardless of the AKT/MAPK/mTOR signaling (Li et al., 2018b, 2019). Ginsenoside Rg3 was found to attenuate isoproterenol-induced myocardial infarction in the mouse heart injury model by activating autophagy via AMPK/mTOR signaling (Sun et al., 2020).

Under conditions of cellular stress, the activation of autophagy might be favorable, since it improves the removal of misfolded or aggregated proteins, beyond the damaged mitochondria related to heart inflammation (Yamaguchi, 2019). As revealed by preclinical studies, the drugs sulfaphenazole (Huang et al., 2010) and chloramphenicol (Sala-Mercado et al., 2010) might promote cardioprotection by autophagy activation, with the consequent reduction of myocardial damage during ischemia-reperfusion (I/R). It seems that chloramphenicol or its derivatives can induce or facilitate cardioprotection, which depends on the formation of autophagosome (Giricz et al., 2017). Trehalose reduces the induction of cardiac remodeling after myocardial infarction and dysfunction through autophagy activation and upregulation of the transcription factor TFEB (Sciarretta et al., 2018), which also alleviates atherosclerotic plaque burden (Evans et al., 2018). Selenium also has positive effects on the heart (e.g., it contributes to cardiac remodeling after chronic heart failure or protects cardiomyocytes from hyperglycemia-induced heart damage and increased cardiac dysfunction) (Alexanian et al., 2014; Chen, 2012; Steinbrenner et al., 2016; Liu et al., 2013b), and these effects appear to be related to the regulation of protective autophagy (Chen et al., 2019).

Autophagy contributes to cellular cholesterol efflux and cholesterol ester (CE) hydrolysis, processes that break down lipid droplets by foam cells (He et al., 2017; Gu et al., 2016). Restoration of autophagic flux by nicotinate-curcumin may alleviate atherosclerosis (Gu et al., 2016). CTRP9 is an adipokine agonist of adiponectin receptor 1 (ADIPOR1) that displays a regulatory function in lipid metabolism. Administration of recombinant CTRP9 (rCTRP9) protects against atherosclerosis by promoting cholesterol efflux that reduces foam cell formation cells through autophagy induction in a manner dependent on the AMPK/mTOR signaling pathway (Zhang et al., 2018b). Then, rCTRP9 might be used to alleviate atherosclerosis and CVD through autophagy regulation, and efforts should be made to further investigate this premise.

Aside from autophagy inductors, pharmacological inhibitors also are used to treat cardiac disorders. *In vitro* and *in vivo* studies demonstrated that the inhibitor of histone deacetylases trichostatin A (TSA) alleviates cardiac hypertrophy by suppressing autophagy, leading to reduced pathologic cardiac remodeling during severe pressure overload (Cao et al., 2011) or after myocardial infarction (Wang et al., 2018). The effects of TSA are probably related to an increase in STX17 acetylation, leading to suppression of autophagosome maturation (Shen et al., 2020). The natural compound allicin also mitigates cardiac hypertrophy in the abdominal aortic constriction model through activation of PI3K/AKT/mTOR and MAPK/ERK/mTOR signaling, resulting in relief of myocardial autophagy (Ba et al., 2019).

Through harmful modulation of the early stage of autophagic machinery related to inhibition of Beclin 1 expression, propofol reduces cell death caused by myocardial I/R injury associated with deactivation of mTOR signaling and enhanced autophagy activation (Noh et al., 2010). Besides, it may prevent cerebral ischemia-triggered autophagy activation and cell death through the NF-κB/p53 signaling pathway (Cui et al., 2013). A recent report shows that propofol significantly reduces serum levels of LC3-II and mTOR, which is associated with inhibition of autophagy in myocardial cells from rats with type 2 diabetes mellitus (Wang et al., 2020b). Berberine and melatonin are potential drugs to prevent excessive autophagy in cardiomyocytes via suppressing upstream AMPK signaling, which leads to amelioration of cardiac ischemia/reperfusion injury (Huang et al., 2015; Chen et al., 2018c). However, the melatonin effect on autophagy might also be related to its activation through the AMPK/mTOR/ULK1 axis, which is associated with a decrease in calcium deposition, osteogenic differentiation, oxidative stress, and apoptosis, which altogether mitigates calcification of vascular smooth muscle cells (Chen et al., 2020b). The widely used anti-ischemic drugs trimetazidine, and hesperidin were found to attenuate myocardial ischemia/reperfusion (MI/R) related to excessive autophagy through activation of AKT/mTOR signaling (Wu et al., 2018; Li et al., 2018c).

Myostatin (MSTN) is a myokine responsible for the negative regulation of muscle growth and has been highlighted as an attractive protective regulator of cardiac function, whose expression was found upregulated in cardiomyocytes following infarct (Sharma et al., 1999). MSTN also may control insulin sensitivity, since it negatively regulates AMPK levels in peripheral tissues (Zhang et al., 2011c). Recently, MSTN was found to significantly alleviate cardiac dysfunction and pathological hypertrophy by reducing enhanced autophagy in cardiomyocytes via suppressing miR-128/PPARγ/NF-κB and AMPK/mTOR signaling pathways (Qi et al., 2020). Thereby, pharmacological (e.g., agonist drugs) or biotechnological (e.g., recombinant proteins) approaches targeting the MSTN upregulation may be useful in treating cardiac dysfunction following pathological hypertrophy or infarction. However, studies should take into account the potential side effects related to MSTN upregulation because skeletal muscle atrophy may occur (Ebner et al., 2015).

Despite these pharmacological interventions to suppress enhanced autophagy activation have been promisor, an extensive comprehension of myocardial autophagy will be required to circumvent the loss of homeostatic mechanisms or probable cardiac-adverse effects. Thus, although significant questions and discussion remain, patients with CVD are likely to benefit from these attempts.

6. Conclusion remarks

As we reviewed here, modulation of autophagy can have beneficial effects in treating age-related diseases such as cancer, neurological, and cardiac diseases. Despite the potential autophagy modulation by pharmacological or genetic intervention described here, its multiple off-target effects make it difficult to conclude that autophagy is the critical target fully. The main obstacles are the absence of specificity of the current drugs that have been used for the uniqueness of targeting autophagy, including those addressing the PI3K/AKT/mTOR pathway and lysosomal function. Additionally, future research concerning age-related diseases with high disability or mortality may rely more on their 'systems biology' approach. Toward this end, it would be necessary to emphasize the interaction of multiple factors such as stressors, metabolic condition,

microbiota, genetic predisposition, inflammatory and immune responses, vascular insufficiency, ischemia-reperfusion, cardiac remodeling, clearance of protein aggregates, and other biochemical anomalies. Thereby, future efforts are required for the development of drugs with increased pharmacologic specificity, as well as the elucidation of autophagic machinery (or thereof components) that seem to have a limited role in other processes. Among all efforts, those focused on the development of novel and more specific autophagy inhibitors/inductors and their integration into therapeutic regimens should remain a priority for the field, at least for the treatment of age-related diseases such as cancer. Such scientific endeavors should not discourage this end, and persistence is required to achieve this global goal.

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CRediT authorship contribution statement

Waleska Kerllen Martins: providing language help, proofreading the article, supervising the review, writing the main manuscript text and drawing the figures, All authors reviewed the manuscript. **Maryana do Nascimento da Silva:** writing assistance, helping in searching preclinical and clinical studies. **Kiran Pandey:** writing assistance. **Ikuko Maejima:** writing assistance. **Ercília Ramalho:** helping in searching preclinical and clinical studies. **Vania Claudia Olivon:** writing assistance. **Susana Nogueira Diniz:** writing assistance, providing language help. **Daniel Grasso:** writing assistance, providing language help, proofreading the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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