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Autophagy: The convergence point of aging and cancer

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A B S T R A C T

Autophagy, a dynamic intracellular degradation system, is critical for cellular renovation and maintaining equilibrium. By eliminating damaged components and recycling essential molecules, autophagy safeguards cellular integrity and function. The versatility of the autophagy process across various biological functions enable cells to adapt and maintain homeostasis under unfavourable conditions. Disruptions in autophagy can shift a cell from a healthy state to a disease state or, conversely, support a return to health. This review delves into the multifaceted role of autophagy during aging and age-related diseases such as cancer, highlighting its significance as a unifying target with promising therapeutic implications. Cancer development is a dynamic process characterized by the acquisition of diverse survival capabilities for proliferating at different stages. This progression unfolds over time, with cancer cells exploiting autophagy to overcome encountered stress conditions during tumor development. Notably, there are several common pathways that utilize the autophagy process during aging and cancer development. This highlights the importance of autophagy as a crucial therapeutic target, holding the potential to not only impede the growth of tumor but also enhance the patient's longevity. This review aims to simplify the intricate relationship between cancer and aging, with a particular focus on the role of autophagy.

1. Introduction

Autophagy is a complex catabolic process which is the basic essentiality of any cell for maintaining homeostasis. The aberration in the autophagy process has been widely studied in various physiological and pathological diseases, including neurodegenerative diseases, aging, and cancer. However, the paradigm shift showed the involvement of autophagy in promoting these diseases as well, making it evident to understand the context-dependent nature of autophagy process [1,2]. The pathways through which autophagy delivers the cargoes to the lysosomes are divided into three types based on the formation of double-membrane autophagosomes, as mentioned in Fig. 1.

Macroautophagy (hereafter referred to as autophagy) involves the formation of autophagosomes comprising of all the degraded cargoes, followed by fusing with lysosomes, forming autophagolysosomes or autolysosomes (Fig. 1A) [3]. Y Ohsumi developed mutated yeast lacking vacuolated degrading enzymes that inhibit the fusion step while autophagy is active. The resultant accumulation of autophagosomes, further helps in categorising the cascade of steps involved in autophagy process [4]. This discovery also led to functionally characterizing the genes involved in autophagosome formation. Mechanistically, under starvation or calorie restriction, there is inhibition of mTOR (mammalian target of rapamycin) and activation of AMPK (AMP-activated protein kinase). This, in turn, leads to the phosphorylation and activation of ULK1 (Unc-51 like autophagy activating kinase 1), a key initiator of autophagy. Moreover, ULK1 interacts with Atg13, which directly binds to FIP200 and further activates downstream Atg genes, forming a ULK1/2 complex for initiating the nucleation stage that includes ULK1/2 (mammalian homologs of Atg1), ATG13 (a homolog of yeast Atg13), RB1CC1/FIP200 (a putative Atg17 homolog), and C12orf44/ATG101 (the latter component is not conserved in S. cerevisiae). ULK1 activates the AMBRA1 and BECN1 components of the phosphoinositide 3-kinase complex. Class III Ptd3k consists of PIK3C3, PIK3R4, and BECN1, which are part of at least three different components. BECN1 binds to AMBRA1 after release from the BECN1-BCL2 complex and activates Atg14. UVRAG further replaces Atg14 and forms the UVRAG-AMBRA1 complex, along with its positive regulator SH3GLB1, which continues the development of the autophagosome [3]. Further, ATG9, an integral membrane protein essential for autophagy, is recruited to pre-autophagosomal structure by interacting with ATG17 in ATG1 dependent manner [5].

During the phagophore expansion, two ubiquitin protein conjugation

Abbreviations: ROS, Reactive oxygen species; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; ULK1, Unc-51 like autophagy activating kinase 1; PAMPs, pathogen-associated molecular patterns; NSCLC, non-small cell lung cancer; CSCs, cancer stem cells; DAMPs, damage-associated molecular patterns.

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systems come into play. The ubiquitin protein conjugation system is highly conserved from yeast to mammals. The homologs of Atg8 are LC3 and GABARAP, wherein LC3 is involved at the stage of phagophore elongation and GABARAP comes in later stages of maturation. The homolog of Atg4, Atg4B, is a cysteine protease that cleaves the C-terminal arginine residue of the pro-LC3, forming LC3-I that further undergoes post-translational modifications to be subsequently conjugated by PE to generate membrane-associated LC3-II [6].

The conjugation of LC3-PE happens by the Atg12-Atg5-Atg16 ubiquitin protein conjugation system [7].

The completed autophagosomes, but not the isolated membrane phagophore, contain Stx17 that binds to SNAP-29 and lysosomal SNARE Vamp 8, further aids in the fusion [5]. The autophagosome further fuses with lysosomes via recruiting lysosomal fusion proteins, and the already attached ATG proteins to the membrane of the autophagosomes are eventually removed. Understanding this macromolecular complex by dissecting each step and monitoring the interactions of different proteins in the autophagy process offers profound insights into therapeutic targeting for various diseases [8]. It's also crucial to understand whether autophagy's role within the cellular system is predefined or evolves overtime, in the context of aging and tumor development. This connection is critical, as older patients often experience heightened side effects from anticancer treatments, raising concerns about their quality of life. This review consolidates key findings to illustrate how autophagy interconnects the complex, age-related processes of cancer and aging, with a stepwise analysis covering autophagy's roles in the interplay between aging and cancer.

2. Aging and cancer: A complex interplay

Aging involves gradual accumulation of deleterious changes in cells and tissues resulting in impaired cellular functions and eventually leading to death. Likewise, advancing age is a major risk factor for cancer development, driven by encountered unwanted mutations, compromised DNA integrity, and accumulation of toxins [9]. Although aging and cancer are intricately interconnected, recent research has emphasized the non-linear dimension underlying aging and cancer. It was reported by Wang et al. that the survival of pancreatic cancer patients has an inverse relationship with age [10]. However, an increase in the uncommon "early onset" of cancer risk is also observed in young populations [11]. As recently reported by X Zhuang et al., the aging-associated increase in stemness posited to suppress tumorigenesis by aging-associated induction of transcription factor NUPR1, which leads to iron insufficiency in the aged cells. The time-dependent development of cancer and aging share several essential characteristics and are the common "meta-hallmarks" [12].

i) Telomeres and Genomic instability

One key factor linking aging and cancer is telomere length maintained by telomerase enzyme. Telomeres are protective caps at the ends of chromosomes that shorten with each cell division. This can lead to genomic instability, irreversible cell cycle arrest (senescence), or cell death. To achieve cellular immortality, cancer cells such as lung cancer cleverly circumvent replicative senescence and cell death by reactivating telomerases [13,14]. However, the relationship between telomere length and cancer risk is complex. While some studies suggest that longer telomeres may increase cancer risk in certain populations, others indicate that telomere shortening can also contribute to cancer development by increasing genomic instability. Calado et al. discovered short telomeres and loss-of-function mutations in the TERT and TERC genes in acute myeloid leukemia, gastrointestinal tumors, and head and neck

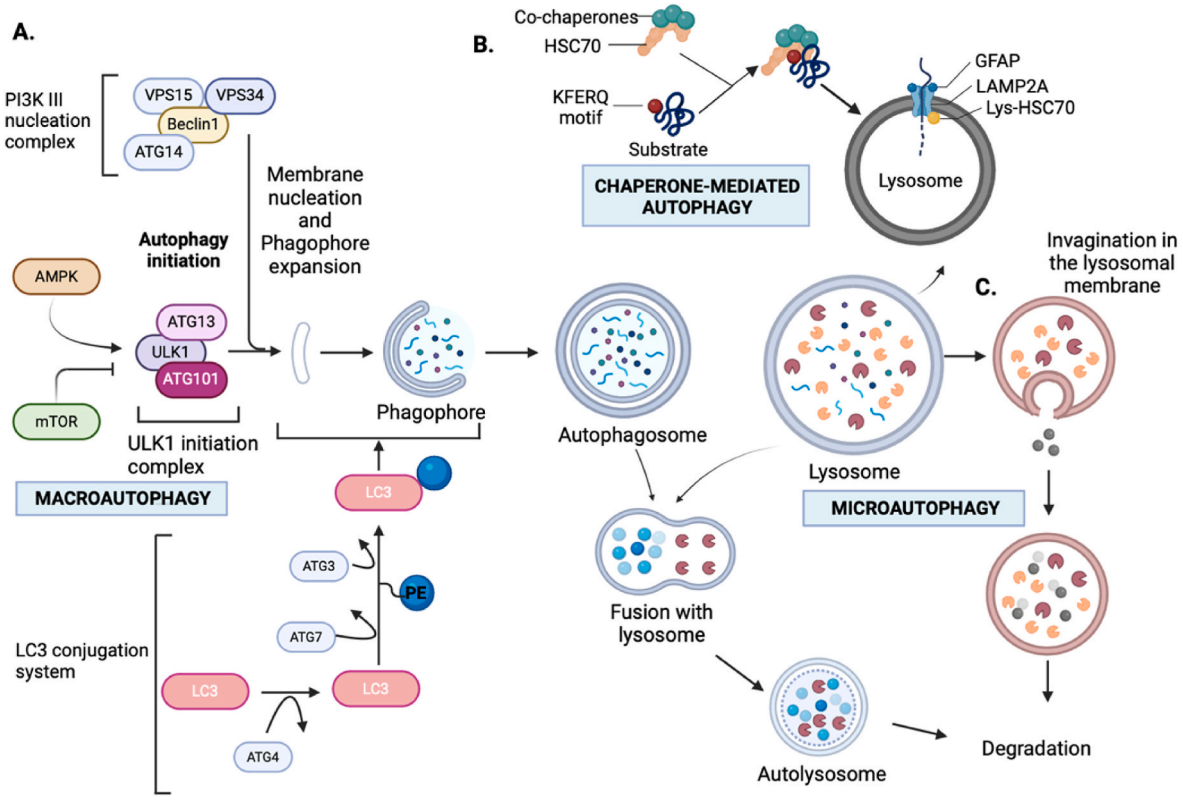

Fig. 1. Types of autophagy. Autophagy is divided into three types on the basis of double membrane autophagosome formation. **A.** The most commonly studied autophagy in cancer cells is macroautophagy. It involves a four step process: 1. Nucleation 2. Pre-autophagosome formation 3. Autophagosome formation 4. Autophagosome and lysosome fusion and autolysosome formation. **B.** Chaperone mediated autophagy includes engulfment of substrates with KFERQ motifs recruited by HSC70 and co chaperones to lysosomes. **C.** Microautophagy includes direct engulfment of substrates into lysosomes.

cancer [15,16]. Interestingly, exposure of cancer cells to aged fibroblasts can lead to the secretion of sFRP2, a Wnt pathway antagonist, which disrupts microphthalmia transcription factor (MITF) and β-catenin signaling. This disruption further reduces APE1 expression, which promotes angiogenesis and metastasis in melanoma cells [17].

The decline in the expression of APE1/Ref-1(involved in base excision repair), with age, contributes to increased genomic instability in aging cells [18]. Parallel to this, Li et al. found that decreased APE1 levels in cancer cells also increase senescence, which can be a potential therapeutic target addressing both cancer and aging. This dual impact is underscored by the role of ROS, which is a major link between these diseases [19]. Xia et al. observed that ROS produced by ovarian and prostate cancer cells can regulate the expression of hypoxia-inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF), which can lead to the induction of angiogenesis and tumor growth promotion [20]. Additionally, ROS also activates the NF-κB, which can promote senescence-associated secretory phenotype (SASP) which is a significant player in aging [21,22].

ii) Epigenetic Alterations

Epigenetic alterations, involve changes in gene expression without altering the DNA sequence, and play a significant role in both aging and cancer. These alterations include DNA methylation, histone modifications, and involvement of non-coding RNAs [23].

DNA methylation has proven to be a complex link between aging and cancer. Increased aberrant hypermethylation with aging was observed in several CpG-island-containing genes, leading to cancer predisposition [24]. Conversely, global hypomethylation of repeat elements, an epigenetic signature of cancer, also increases with aging [25,26]. In aging, enriched DNA hypomethylation was observed at genomic regions containing H3K4me1, which is an activating histone modification. On the other hand, the loss of DNA methylation in cancer was associated with H3K9me3, a repressive histone mark [27]. Deficiency of epigenetic enzymes also has a huge influence on cancer and aging. Bonkowski and Sinclair reported that a decrease in the activity of histone deacetylases like sirtuins can lead to increased chances of DNA damage, leading to cancer and aging because of increased chromatin relaxation [28]. The human SIRT6 protein, which is an NAD + -dependent histone H3 lysine 9 (H3K9) deacetylase, can further add to the telomeric deregulation discussed earlier by modulating telomeric chromatin [29]. Various sirtuins can also positively regulate epithelial-to-mesenchymal transition (EMT) and metastasis. For example, SIRT1 leads to EMT by cooperating with EMT-inducing transcription factor ZEB1 in prostate cancer cells [30]. The deregulation of the nutrient-sensing pathways is another important factor. Several studies have proved that mutations activating or inactivating essential nutrient-sensing genes like PIK3CA and liver kinase B1 (LKB1) can lead to cancer [31,32].

iii) Deregulation of Nutrient-Sensing Pathways

Calorie restriction, which can influence various nutrient-sensing pathways, has also been reported to prevent tumor formation [33] and to slow down the age-dependent down-regulation of many cellular processes [34]. An interesting observation was reported by Zitvogel et al. that our normal gut microbiota also has an important role to play in aging and cancer. Gut microbiota disturbance, or dysbiosis, may lead to chronic inflammation [35]. Dysbiosis and aging can lead to 'inflammageing,' which causes several age-associated diseases [17] and a reduction in the effectiveness of tumor immunosurveillance [36].

Further research is crucial to fully understand this intricate interplay and develop effective strategies to promote healthy aging and prevent cancer.

3. Autophagy and aging

Autophagy is essential for cellular health, contributing to extended longevity and slower aging. Additionally, normal aging is associated with a decline in autophagic function, leading to the accumulation of harmful substances and cellular damage [37].

i) mTOR, a central nutrient regulator

Autophagy, when activated by starvation or calorie restriction, supplies essential raw materials, removes ROS, and supports cellular health (Fig. 2). mTOR, a major player that inhibits autophagy, is a central node in the network, channeling nutrients for cell growth [38]. Dysregulation at any step disturbs homeostasis and ignites the malfunctioning of aging-associated metabolic pathways. Activation of autophagy by genetically or pharmacologically inhibiting mTOR (by rapamycin) can enhance the degradation of aged cellular components. mTOR was known to cripple the early stages of the autophagy process under nutrient-available conditions [39]; however, in 2015, Young-Mi Kim et al. showed that mTOR inhibits later stages of autophagy as well by phosphorylating UVRAG, promoting the binding of RUBICON that further inhibits the UVRAG-mediated autophagosome maturation [40]. Inhibition of mTOR by deprivation of nutrients or by rapamycin treatment shifts from the biosynthesis of raw materials to providing recycled raw materials using autophagy machinery, which promotes age-related decline in tissues in yeast, C. elegans, and D. melanogaster. The use of rapamycin to slow the aging process is currently being studied to evaluate its longevity benefit at different drug doses [41].

While mTOR regulates various pathways, including protein synthesis, it remains unclear whether autophagy induction through stress-induced mTOR inhibition alone or in conjunction with mTOR regulatory pathways like mRNA translation, mitochondrial dysfunction, contributes to extended tissue lifespan.

ii) AMPK Activation

mTOR and AMPK have contrasting roles in the induction of autophagy [39,42,43]. Contrary to mTOR, AMPK positively regulates the autophagy process and produces distinct outcomes for aging. When the ADP/ATP ratio increases during nutrient-deficient conditions, AMP interacts with the gamma subunit of AMPK to activate it. AMPK further forms a stable complex with ULK1 and is followed by phosphorylating it. ULK1 is a kinase that triggers key molecular events of pre-autophagosome formation and activates the Atg14-associated Vps34 complex [44]. Despite the widespread acceptance of the prevailing model, a paradigm shift model suggests that the phosphorylation of S758 disrupts the interaction of AMPK and ULK1. However, the new model suggests that phosphorylation of ULK1 at S758 maintains a stable association with AMPK that protects ULK1 degradation at starvation or mTOR inhibition [45].

Furthermore, the activation of AMPK in the adult Drosophila nervous system induces autophagy in the brain by upregulating the autophagy-specific kinase Atg1, resulting in better intertissue effects during aging and an extended lifespan. The AMPK/Atg1-mediated autophagy activation is linked to a reduced insulin/insulin-growth factor-1-signaling (IIS) pathway. Repressed IIS promotes the translational regulator 4E-BP, a direct target of dFOXO (Drosophila FOXO), slows systemic aging, and prolongs lifespan [46].

iii) Lysosomal Degradation

Autophagy relies on lysosomes' provided acidic pH to degrade cellular components. Lysosomal function declines with age, contributing to the accumulation of damaged proteins and organelles. This decline in lysosomal activity is mitigated in long-lived mutants, suggesting that maintaining lysosomal function is crucial for longevity [47]. In C.

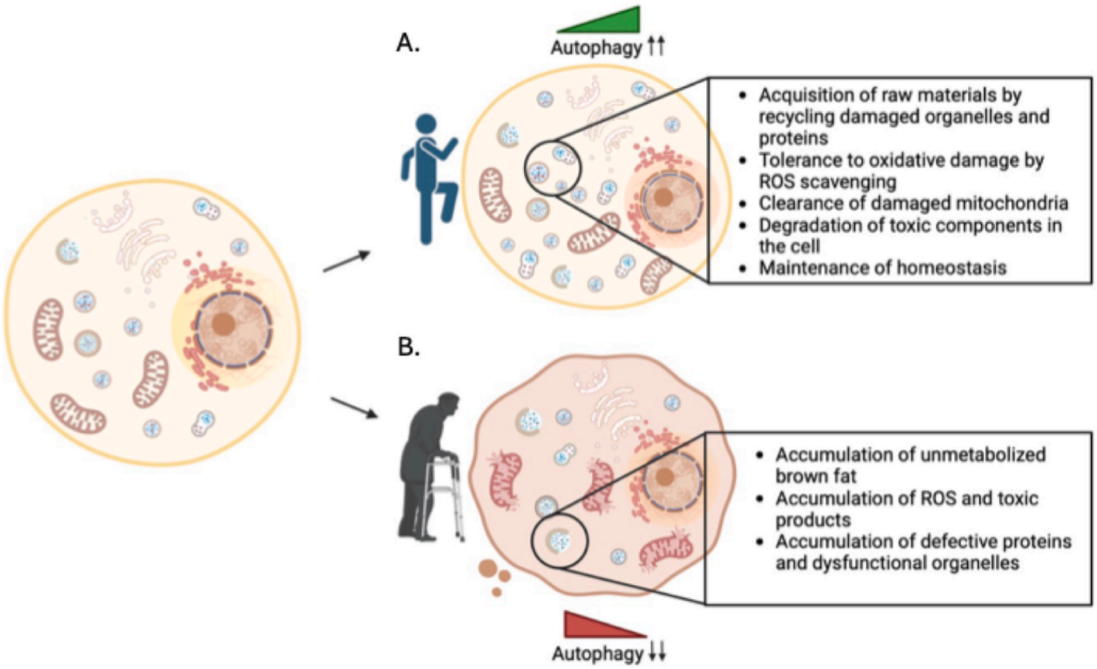

Fig. 2. Autophagy in young versus aged cells. A. Increase in autophagy in young cells. Role and mechanism of autophagy mediated maintenance of slow aging in young cells.; B. Decrease in autophagy in old cells leading to aging.

elegans, mice, and Drosophila, a decline in protease activity has been observed with age [37]. Notably, Yanan Sun et al., in 2020 demonstrated that age-associated lysosomal activity changes are mitigated in long-lived mutants (daf-2, eat-2, and isp-1) that extend the lifespan by mechanisms involving inhibiting insulin/IGF-1 signaling, reducing food intake, and impairing mitochondrial function [48]. Additionally, Richard Venz et al., in 2021 showed that engineered C. elegans with conditional depletion of the DAF-2 transmembrane receptor doubled lifespan during geriatric ages [49]. Moreover, the transcription factor EB regulates various aspects of autophagy, where overexpressed HLH-30, the orthologue of the TFEB gene in C. elegans, results in an extended lifespan. In 2023, Lu Zhang et al. reported on the role of CD44 function in bridging autophagy with the decline in longevity [50].

iv) Autophagy and Neurodegenerative Diseases

Dysregulation of autophagy is implicated in various age-related diseases, including neurodegenerative disorders. The expression of the autophagy-related gene Atg8a in older fly brains extends the average adult lifespan by 56 % and promotes resistance to oxidative stress. However, the mutation of Atg8 results in a reduced lifespan, IUP accumulation, and increased sensitivity to oxidative stress [51]. Hypothalamic autophagy reduction and elevation of α-MSH levels lead to an increase in aged-mice phenocopy, which includes altered glucose homeostasis in proopiomelanocortin (POMC) neurons, increased adiposity, and impaired lipolysis. Enhancing autophagy in these models can extend lifespan and improve neuronal function.

v) Autophagy and Apoptosis

Autophagy and apoptosis represent two opposing processes in the cellular environment, akin to the two sides of the same coin. While autophagy promotes cell survival by removing damaged components, apoptosis eliminates damaged or unnecessary cells. The balance between these processes shifts with age, with autophagy generally declining and apoptosis potentially increasing.

Using Wistar mice, the levels of autophagy and apoptosis were observed to be opposite in the adult and old phases. The adult mice, as compared to older mice, showed a higher autophagy-related *p*-ULK, *p*-ULK-1/ULK-1 ratio, Beclin-1, LC3II, and maintained normal learning and cognitive function. Similarly, a naked mole-rat (NMR) that carries the cancer resistance trait showed higher levels of BECN1, LC3-I, and LC3-II in the brain as a function of age. The higher level of autophagy throughout their lifespan may contribute to the healthy lifespan of these rodents [52].

vi) Autophagy-Related Genes and Aging

Various stimuli activate the autophagy-based type III PI3 kinase. Based on the results of a genome-wide screen, Lipinski et al. showed that ROS initiated autophagy by serving as an activator upstream of the type III PI3 kinase in response to amyloid beta peptide, which is the major pathogenic mediator of Alzheimer's disease (AD) [53]. The overexpression of Atg5 in mice increases the lifespan by 17.2 %. Additionally, embryonic fibroblasts developed from Atg5 transgenic mice are more tolerant to oxidative damage [54]. Similarly, Álvaro F Fernández et al. generated targeted mutant mice with a Phe121Ala mutation in BECN1 ($Becn1^{F121A/F121A}$), decreasing its interaction with the negative regulator BCL2. As a result, the knock-in mice showed a higher level of cellular autophagy than their wild-type littermates, with increased longevity [55].

vii) Sirtuins and Autophagy

The sirtuin-1 enzyme, from Sirtuins family, is deeply involved in gene regulation, genome stability maintenance, apoptosis, autophagy, senescence, proliferation, aging, and tumorigenesis [28]. A novel discovery by Michan and Sinclair in 2007 reported the involvement of sirtuins in extending the human lifespan. Wang et al. reported in 2021 that SIRT1 acts as a substrate for autophagosomes, resulting in its degradation in autolysosomes and impacting the aging of cell tissues. The level of SIRT1 decreases with age, which coincides with the decrease in the autophagy process in aging cells [55]. However, in 2023, Chaudhary et al. reported that sirtuin-activating compounds can

upregulate the autophagy process, which helps degrade unwanted toxic cellular components and maintain homeostasis in aging cells [56]. This complex relationship highlights autophagy's dual role in regulating cellular aging, and the following section discusses how autophagy influences the age-dependent disease, cancer.

4. Autophagy and cancer

The perpetual evolving cancer cells have adeptly exploited the autophagy machinery to overcome stressful conditions by utilizing the provided raw materials. Additionally, autophagy has also garnered widespread interest by restricting tumorigenesis induced by calorie restriction, starvation, or stress conditions at the early stages of tumorigenesis, indicating autophagy encompasses both tumor suppressor and promoter aspects (Fig. 3). This dual shows the context-dependent nature of autophagy during tumorigenesis (Table 1).

i) Autophagy and DNA Repair

Autophagy is the process that continuously replenishes DNA repair enzymes in the cells and maintains double-stranded breaks that, if left unrepaired, can lead to oncogenic mutations [57]. Wadsworth et al., in 2007, mentioned the monoallelic deletion of BECN1 resulted in a DNA damage response and gene amplification, facilitating breast cancer progression [58].

ii) Autophagy and the Tumor Microenvironment

The tumor microenvironment comprises of stromal cells, extracellular matrix, tumor-associated macrophages, T and B lymphocytes, and immune cells. Autophagy influences the tumor microenvironment by modulating immune responses and providing metabolic support to cancer cells [75,76].

iii) Autophagy and Cancer Cell Metabolism

Autophagy provides metabolic substrates by degrading cellular components that fuel cancer cell growth and proliferation. The key difference between tumor and normal cells relies on cellular metabolism. Normal cells undergo oxygen-dependent oxidative phosphorylation (OXPHOS) to produce ATP; however, cancer cells switch towards glycolysis, and the intermediates rewire to biosynthetic pathways such as the pentose phosphate pathway. Autophagy still maintains mitochondrial integrity despite its negligible requirement for ATP production in cancer cells [62]. The deletion of ATG7 in $BRAF^{V6000E}$-driven lung cancer cells results in a deficiency of glutamine, an essential raw material for mitochondrial respiration and survival of tumor cells driven by $BRAF^{V6000E}$. Interestingly, autophagy inhibition results in the accumulation of damaged mitochondria that promotes the survival of cancer cells, such as mammary cancer cells, which results in increased ROS levels switching oxidative to the glycolytic metabolic pathways [77].

iv) Autophagy and EMT

EMT is a complex transdifferentiation process through which cancer cells acquire mesenchymal potential. Autophagy activation is indispensable during metastatic spreading to resist the cell death pathways activated due to a lack of adhesion with the extracellular matrix, leaving

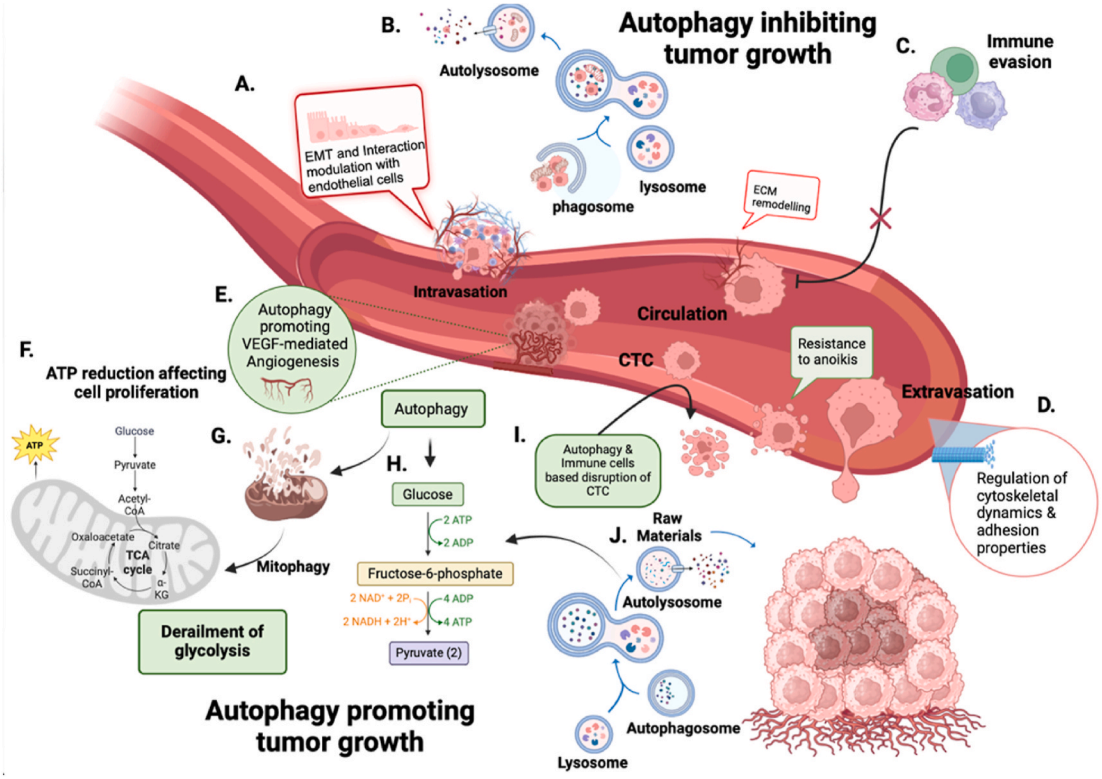

Fig. 3. Dual role of autophagy in tumor progression. Autophagy inhibits tumor progression. A. Autophagy induction during the intravasation of cancer cells, inhibiting EMT through increasing E-cadherin and decreasing N-cadherin. **B.** Autophagy engulfing intracellular mutants, damaged mitochondria, and infectious pathogens using autophagosome formation followed by degrading it in autolysosomes. **C.** Autophagy decreases the immune evasion of cancer cells by promoting pathogen clearance. **D.** autophagy recruiting cytoskeletal components and inhibiting the migration of cancer cells. **Autophagy promotes tumor development. E.** Autophagy-mediated increase in VEGFA and pro-angiogenic pathways. **F.** Autophagy diverting dependence of cancer cells over OXPHOSfrom glycolysis when treated with glycolytic inhibitor. **G.** partially degrading mitochondria and maintaining defective mitochondria in cancer cells. **H.** Autophagy promotes glycolytic pathways **I.** BNIP3 and BECN1 promote autophagy and resistance to anoikis. **I.** Autophagy promotes immune tolerance in cancer cells by inhibiting immune checkpoints and antigen presentation. **J.** Autophagy mediated recycling of toxins and providing raw materials for tumor development.

Table 1
Pro- and anti-tumorigenic roles of autophagy.

Factors regulating tumorigenesis	Pro-tumorigenic roles of autophagy	Anti-tumorigenic roles of autophagy
PI3K/Akt/mTOR pathway		Induction of autophagy by inhibiting the PI3K/Akt/mTOR pathway can prevent cancer growth [59]
NF-κB signaling	The accumulation of ROS, p62, damaged mitochondria, and endoplasmic reticulum chaperones due to defective autophagy alters NF-κB signaling and promotes tumorigenesis [60]	
Glycolysis	Promotion of glycolysis by supplying substrates through recycling of cellular components during nutrient scarcity, thus promoting cancer cell survival [61]	
Oxidative phosphorylation	Enhanced autophagy in cancer cells promotes mitochondrial OXPHOS to increase ATP production which is required for cancer cell survival [62]	
DSB repair		Replenishment of DNA repair enzymes in the cell which repair double-strand breaks, thus preventing oncogenic mutations [57] Degradation of DNA fragments and clearance of proteins associated with DNA repair during DSB repair, which lead to the maintenance of accuracy and proper functioning of DNA repair pathways [57]
Homologous recombination		Activation of Chk1, which is linked to DNA repair by homologous recombination [63]
Cell cycle checkpoints	Suppression of proteins associated with cell cycle checkpoints such as p53 and p21, which can lead to oncogenesis [64,65]	Modulation of cell cycle responses by preventing unrepaired cells from continuing to divide, and thus preventing oncogenesis [66]
Immune response	Attenuation of the target cell's immunologic synapse with cytotoxic T lymphocytes, thus inhibiting CTL-mediated tumor cell lysis [67]	Activation of cytotoxic responses by the enhancement of antigen presentation in dendritic cells and the induction of $CD8^+$ lymphocytes [67] Clearance of aberrant Treg cells that inhibit the immune response [67] Providing raw materials for maintaining the efficiency of immune cells [67]
Drug resistance	Increase in drug resistance by managing the stress caused due to anticancer drugs, removing damaged organelles, recycling essential nutrients, and avoiding apoptosis [68]	
Survivability of cancer cells	Promotion of cancer cell survival at the tumor core under stress conditions like low oxygen and nutrient unavailability [69] Providing raw materials for cancer cell growth by the release of recycled molecules after the degradation of damaged cellular components [70]	
Angiogenesis	Promotion of angiogenesis during stress conditions like nutrient deprivation and hypoxia by enhancing the secretion of VEGF, survival of endothelial cells, and modulation of tumor microenvironment [71]	Suppression of angiogenesis by degradation of pro-angiogenic factors and normalization of blood vessels [72]
ECM remodelling	Degradation and recycling of ECM components [73] Regulation of the production of matrix metalloproteinases (MMPs) which facilitate ECM remodelling [73] Secretion of ECM proteins [73]	
Epithelial-to-Mesenchymal Transition (EMT)	Resisting induction of apoptotic pathways activated due to a lack of cell adhesion to the extracellular matrix during EMT [74]	
Metastasis	Providing resistance to nutrient deprivation, hypoxic conditions and immune surveillance during metastasis [73]	

cells without effective anchorage [57,78]. Fung et al. showed that extracellular matrix detachment from cells induces autophagy, whereas deprivation of ATGs inhibits detachment-induced autophagy, enhances apoptosis, and reduces clonogenic recovery after anoikis [79].

v) Autophagy and Immune Evasion

Autophagy's dual role is experienced by cancer cells when it can use immune cells to impede tumor growth and, on the other hand, escape cancer cells from immune cell attacks. Akalay et al. showed that MCF7 breast cancer cells showed EMT phenotypes, including inhibiting cytotoxic T lymphocyte-mediated tumor cell lysis [80]. EMT, along with invasion and metastasis, also alters the susceptibility of cancer cells by inducing autophagy that attenuates the immunologic synapse with CTL in the target cells [67].

All these studies provided evidence of the context-dependent role of autophagy, influencing the fate of the tumors at various stages. However, the precise mechanism and contribution of autophagy process during cancer progression still remain to be fully elucidated.

5. Autophagy features affect tumorigenesis in each cancer types

5.1. Lung cancer

Lung cancer ranks among the foremost causes of mortality for both men and women globally [81]. According to various reports, autophagy plays a dichotomous role in upregulation and downregulation of lung cancer based on stage [82]. Recent reports are primarily focused on non-small cell lung cancer (NSCLC) which accounts for approximately 85 % or mortality rate [83]. Several reports have indicated the higher concentration of specific proteins such as TIPRL in NSCLC actively promoting autophagy, and enhancing cancer cell survival. The increased TIPRL expression interacts and phosphorylates eIF2α, that induces autophagy by the activation of the eIF2α-ATF4 pathway. This autophagy

activity facilitates the clearance of metabolic and cellular stress, providing a survival advantage to cancer cells [84]. NSCLC stem like cells (CSC) represent a distinct yet closely related area of research, particularly concerning the role of autophagy in facilitating cancer cell proliferation. It was recently reported on how TGM2, which is increased in $CD44^{+}$ A549 stem-like cells, facilitates radio-resistance in NSCLC via augmenting autophagy. The CD44-TGM2-LC3 axis was identified, wherein CD44 facilitates radio-resistance via TGM2 modulation of autophagy. TGM2 interacts with LC3B, a pivotal autophagy protein, to regulate autophagy levels, therefore safeguarding cancer stem-like cells from radiation-induced harm. This indicated TGM2 as a prospective therapeutic target to mitigate radio-resistance in NSCLC cancer stem-like cells [85]. Considering the inhibitory outcomes of autophagy in cancer progression, SLL-1A-16, a new organic selenocyanate compound has been recently developed and evaluated for the treatment of NSCLC both *in vitro* and *in vivo*. The findings indicate that SLL-1A-16 suppressed cell cycle, promoted apoptosis, and induced autophagy in NSCLC cells by targeting the Akt/mTOR signalling pathways [86]. Another study has shown regarding a natural product Gitogenin (GIT), a saponin derived from *Tribulus longipetalus*, inhibiting lung cancer progression by inducing both apoptosis and autophagy. GIT reduces the proliferation of lung cancer cells and induces apoptosis by increasing the cleavage of Caspase-3 and PARP. It also initiates autophagy by activating AMPK and blocking AKT signalling pathways, leading to the accumulation of autophagosomes. However, GIT disrupts autophagic flux, causing impaired auto phagolysosomes to accumulate, which sensitizes lung cancer cells to cell death (Table 2) [87]. Thus, autophagy plays a dual role with respect to lung cancer progression.

The role of autophagy has been widely studied for facilitating metabolic adaptability by reutilizing cellular constituents, including impaired organelles and misfolded proteins, to supply vital nutrients and energy [98]. In NSCLC, autophagy enhances the TCA cycle and nucleotide synthesis, especially in KRAS-driven malignancies, by promoting the recycling of glutamine and glutamate [99]. Within the tumor microenvironment (TME), autophagy facilitates the metabolic requirements of cancer stem cells (CSCs) and influences immunological responses, angiogenesis, and extracellular matrix remodelling. It interacts with reactive oxygen species (ROS), eliminating damaged organelles to mitigate oxidative stress and avert DNA damage, therefore facilitating tumor survival [100]. Recent research has displayed on how Cadmium helps in the growth of lung cancer cells via autophagy dependent glycolysis. Cadmium exposure in A549 lung cancer cells and HELF lung fibroblasts elevates glucose absorption, lactate generation, and the expression of critical glycolytic enzymes (GLUT1, HKII, PKM2, and LDHA), resulting in augmented glycolysis. The metabolic transition relies on autophagy, as restriction of autophagy (via 3 MA, CQ, or knockdown of ATG4B and ATG5) diminishes glycolysis that impedes Cd-induced cellular proliferation and cell cycle advancement. The study emphasizes an autophagy-glycolysis axis, in which autophagy enhances cancer cell survival by facilitating glycolytic metabolism, positioning it as a possible treatment target for lung cancer [101]. Similarly, when lung cancer cells were exposed to cadmium (Cd), it resulted in the overexpression of HMGA2 that augments the glycolysis while inhibiting the OXPHOS, leading to elevated glucose consumption and lactate formation. Inhibition of autophagy (via 3 MA) reinstates OXPHOS and reduces glycolysis, signifying that autophagy is crucial for this metabolic transition. This metabolic transformation facilitates Cd-induced lung cancer cell migration and invasion, indicating that targeting HMGA2 and autophagy-dependent glycolysis may represent a viable treatment strategy [102].

Autophagy significantly contributes to immune evasion in lung cancer by regulating both innate and adaptive immune responses. Within the tumor microenvironment (TME), autophagy facilitates cancer cells in circumventing immune recognition by destroying damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), which are essential for triggering innate immune responses [103]. Interestingly, several studies have reported the association of chemokines with autophagy in regulating immune evasion. It is found that autophagy facilitates immune evasion in lung cancer via regulating the SKIL/TAZ axis and inhibiting the STING pathway. SKIL expression is heightened in NSCLC and promotes malignant characteristics by upregulating TAZ, which subsequently activates autophagy. The stimulation of autophagy suppresses the STING pathway that results in diminished synthesis of immune-activating chemokines (CXCL10, CCL5, and IFN-β). Additionally, activation of autophagy also leads to reduction in the infiltration of cytotoxic T cells. Inhibiting SKIL or autophagy reinstates STING activation, augments T cell infiltration, and bolsters anti-tumor immunity [104]. In conclusion autophagy plays a vital role in regulating immune evasion in lung cancer.

Table 2
Therapeutic targets indicating cancer-specific function of autophagy.

Cancer type	Drug	Mode of action
Breast Cancer	Everolimus	Induction of autophagy by inhibiting mTOR [88]
	Palbociclib	Induction of autophagy by Inhibiting CDK4/6 [88]
	Gemcitabine Nab-paclitaxel Chloroquine Hydroxychloroquine	Inhibition of autophagy [88]
Pancreatic Cancer	Everolimus	Induction of autophagy by inhibiting mTOR [89,90]
	Chloroquine Hydroxychloroquine	Inhibition of autophagy [91,92]
Colorectal Cancer	3-methyladenine (3-MA) Hydroxychloroquine	
	Salidroside	Induction of autophagy and apoptosis through the PI3K/Akt/mTOR pathway [93]
Glioblastoma	Temozolomide	Modulating autophagy and mitochondrial metabolism [94]
Prostate cancer	PD-PSL1-CP	Inhibition of autophagy [95]
	Apalutamide	Androgen receptor antagonist inducing autophagy [96]
	Simvastatin	Autophagy inducer [97]
Lung cancer	SLL-1A-16	Cell cycle suppression, Apoptosis promoter and Autophagy inducer [86]
	Gitogenin	Inducing apoptosis and autophagy [87]

5.2. Breast cancer

The first significant report linking autophagy to breast cancer was published in 1999 by Beth Levine's group, where they had shown that BECN1 acts as a tumor suppressor protein, which was found to be deficient in breast cancer cells, thus indicating a role of autophagy in breast cancer [105]. However, the role of autophagy in regulation of cancer hasn't been consistent, as its role is been widely studied in both the promotion and inhibition of tumorigenesis. BECN1, an essential gene for autophagosome formation is found to be monoallelically deleted in breast cancer, indicating negative correlation between autophagy and breast cancer progression [106]. Contrastingly, under conditions of metabolic stress, autophagy actively promotes the cancer cell survival [61]. Though it is reported that the genetic deletion of autophagy-related genes reduces primary mammary tumor growth, it was found in a study by Marsh et al. that autophagy restricts the metastasis of disseminated tumor cells (DTCs), where an increase in the size of metastatic lesions was observed upon deletion of Atg12 or Atg5 [107]. Hypoxic stress also leads to the induction of mitophagy responsible for preventing increased levels of reactive oxygen species (ROS) reducing cell death [108]. Further, hypoxia-induced alternative splicing of the BNIP3L gene was recently reported to induce autophagy in breast cancer cells, thus promoting their survival under hypoxic stress

conditions [109].

Prolonged hypoxic stress also leads to the induction of activating transcription factor 4 (ATF4) in MCF7 and MDA-MB-231 breast cancer cells. ATF4 binds to a cyclic AMP response element binding site in the promoter of LC3B, a key component of the autophagosomal membrane, leading to the upregulation of LC3B, which has an essential role in the induction of autophagy, thus helping breast cancer cells to survive ER stress [110]. Another important peculiarity of autophagy process includes an important role in breast cancer is immune evasion by recycling damaged cellular components, maintaining metabolic stability under stress conditions, and regulating the expression of immune checkpoint proteins like PD-L1 present on the surface of cancer cells, thus preventing the immune system from recognising and killing cancer cells [111]. During the chronic hypoxic conditions (0.1 % of hypoxia) autophagy can be induced by the activation of AMPK or inhibition of the mTOR pathway to promote cancer cell survival. However, autophagy induction in MCF7 and MDA-MB-231 breast cancer cells was also reported to induce endoplasmic reticulum (ER) stress and to cause cell cycle arrest [112]. Thus, a therapeutic approach for breast cancer can be to induce autophagy to promote cancer cell death, or to inhibit autophagy when it exhibits protective effects on cancer cells. Several autophagy inducers like everolimus (mTOR inhibitor) and palbociclib (CDK4/6 inhibitor) (Table 2) are being explored for the treatment of breast cancer, and drugs like gemcitabine/nab-paclitaxel, chloroquine, and hydroxychloroquine (Table 2) are also being used to inhibit autophagy in specific contexts in order to enhance the efficacy of other cancer therapies [88].

5.3. Pancreatic cancer

The role of autophagy in pancreatic cancer depends on several factors including the tumor microenvironment that defines the aggressiveness of the pancreatic cancer. A stressful tumor microenvironment can lead to the activation of numerous pathways for the survival of the tumor cells, such as autophagy, anaerobic respiration, and angiogenesis [113]. Pancreatic cancer is particularly dependent on autophagy, when the primary sites experience stress conditions like nutrient stress and hypoxic stress. Furthermore, the activation of oncogenes due to stress induced autophagy leads to the enhanced tumor metabolism and proliferation. In several cases, inhibition of autophagy results in an increase in ROS production, DNA damage, and metabolic defects leading to a decreased mitochondrial oxidative phosphorylation, that altogether abstain the pancreatic cancer growth [114]. Chemotherapeutic drugs used for pancreatic cancer treatment like gemcitabine can induce autophagy in the cells, restricting the efficacy of the treatment [115,116]. Therefore, autophagy inhibitors can be combined along with gemcitabine in order to enhance its therapeutic potential (Table 2). In a study conducted by Zeh et al., it was reported that autophagy inhibition in patients with high-risk pancreatic ductal adenocarcinoma (PDAC) by hydroxychloroquine in combination with gemcitabine and nab-paclitaxel greatly improved the pathologic tumor response [91]. In 2019, Görgülü et al. studied the significance of Atg5 levels in a Kras-mutant model of pancreatic cancer, and they found that single-allele knockout or shRNA-mediated knockdown of Atg5 enhanced malignant tumor formation and metastasis, whereas homozygous deletion of Atg5 increased acinar-to-ductal metaplasia [117]. In the same year, Yang et al. showed that anti-tumor immunity has a role in pancreatic cancer regression upon autophagy inhibition, as they observed an increased infiltration of macrophages in the pancreatic cancer tumors upon the inhibition of autophagy, which was responsible for the anti-tumor effect [118]. Apart from inhibiting autophagy in patients using chloroquine and hydroxychloroquine, the activation of autophagy using mTOR inhibitors like everolimus has also been tried in pancreatic cancer patients, but the results did not show notable clinical action as single treatment agents (Table 2) [89,90]. More research needs to be conducted in order understand the combinatorial approach of autophagy for better therapeutic impact in pancreatic cancer patients.

5.4. Glioblastoma

Glioblastoma, also known as glioblastoma multiforme (GBM) is an aggressive and common type of malignant brain tumor that originates in brain or spinal cord [119]. GBM accounts for half of all cancerous brain tumors, linked to genetic mutations that disrupt cell growth regulation [120]. Autophagy theorized to play a dichotomous role with respect to cancer progression, is assayed to be highly upregulated in high grade gliomas (HGG), which is evident through upregulated ATGs such as p62, LC3 and Beclin 1 [121]. In vivo studies based on mouse model displayed the suppression of autophagy leading to decreased GBM development [122]. Autophagy helps GBM cells survive under stress conditions such as hypoxia where BNIP3 and BNIP3L are upregulated, nutrient deprivation and chemotherapy by recycling cellular components to maintain energy level and resist apoptosis [123]. A Recent study on astrocyte elevated gene 1 (AEG1) has shown the role of autophagy linking EMT to GBM progression. Autophagy stimulation increases the vulnerability of GBM cells to TGFβ1 mediated EMT by AEG1 activation [124]. The role and mechanism of yes associated protein (YAP) in GBM progression revealed that YAP promotes transcription and translocation of HMGB1 from nucleus to cytoplasm, that further enhances autophagy and GBM progression [125]. To sum up, autophagy stimulates the growth of GBM by causing tumor cells to proliferate, meeting their nutritional needs, shielding them from senescence and apoptosis, increasing their EMT, and shielding them from hypoxia.

Metabolic reprogramming is essential for the maintenance of cancer growth and progression [126]. Recent studies on various metabolic and associated molecular pathways have displayed the role of metabolism in GBM progression [127]. NRBF2 upregulates autophagy through its interaction with the VPS34 complex, which is involved in the early stages of autophagosome formation [128]. This process is vital for cell survival and adaptation, especially under metabolic stress. In GBM, NRBF2-mediated autophagy helps the cells survive irradiation (IR) by providing them with essential nutrients and energy sources. NRBF2-mediated autophagy in GBM does not primarily affect glycolysis but rather enhances oxidative phosphorylation. Through autophagy, NRBF2 provides critical intermediates for the tricarboxylic acid (TCA) cycle, which are then used for OXPHOS to generate ATP more efficiently. The metabolic reprogramming driven by NRBF2 is not just about energy production—it also influences other aspects of cancer aggressiveness, like migration and invasion. As NRBF2 regulates autophagy, it indirectly impacts processes like epithelial-mesenchymal transition (EMT), which is crucial for cancer metastasis and invasion [129]. Another protein SH3GLB1, which plays a vital role in autophagy initiation actively regulate mitochondrial metabolism in GBM. Autophagy modulation by SH3GLB1 supports mitochondrial metabolic function, particularly OXPHOS in GBM cells [94].

Autophagy exerts a multifaceted influence on the tumor microenvironment by affecting the functionality and behaviour of immune cells, frequently serving as a strategy for tumor cells to circumvent immune surveillance and enhance their survival [130]. Autophagy impacts the polarization and functionality of the behaviour of Tumor associated macrophages (TAMs), which frequently displays pro-tumoral roles in GBM microenvironment [131]. For example, the reprogramming TAMs to a tumor-supportive phenotype is often promoted by autophagy mediated release of exosomal microRNAs from glioma cells [132]. The efficacy of T cell-mediated immune responses can be influenced by autophagy in GBM cells as Autophagy can impede the activation and function of T cells by regulating the secretion of immunosuppressive cytokines and the presentation of tumor antigens [133]. This results in a more immunosuppressive tumor microenvironment, which enables GBM cells to evade immune surveillance. In conclusion autophagy plays a pivotal role in evading or regulating the immune system and thus promoting the GBM progression.

As autophagy is now evident as an important coupler to GBM, targeting autophagy-related pathways presents promising therapeutic opportunities in GBM treatment [134]. The recent study that reported SH3GLB1, playing an important role in mediating mitochondrial metabolism is also reported in promoting temozolomide (TMZ) resistance in glioblastoma by modulating autophagy and mitochondrial metabolism (Table 2). It was found that knocking down SH3GLB1 resensitizes resistant glioblastoma cells to TMZ, reducing mitochondrial respiration, ATP production, and mitochondrial membrane potential. Thus, SH3GLB1 functions as a key regulator of autophagy-mediated mitochondrial metabolism, enabling glioblastoma cells to evade TMZ-induced cytotoxicity. This suggests that targeting SH3GLB1 may be a potential therapeutic strategy for overcoming TMZ resistance [94].

5.5. Colorectal cancer

The duality of the autophagy process in colorectal cancer (CRC) has been studied, as it can induce apoptosis and decrease the proliferation of CRC cells, while it can also make CRC cells resistant to several chemotherapeutic agents [135]. The chemotherapeutic resistance conferred to CRC cells is due to the cytoprotective effects of autophagy [136], as during the drug treatment, an increase in autophagy induction in cancer cells results in protection against stress-induced damage [137,138], which is the reason why drugs like 5-fluorouracil (5-FU) often fail to treat CRC [139]. In such cases, the use of several autophagy inhibitors such as 3-methyladenine (3-MA) and hydroxychloroquine (HCQ) has proven to promote 5-FU-induced apoptosis in CRC cells [92]. The efficiency of therapeutic drugs also depends on the metabolic effects in cancer cells, which modulates the autophagy process. It was reported by Li et al. that increased production of lactate in CRC cells led to the expression of RUBCNL, an autophagy enhancer protein, which increased the autophagy flux inside the CRC cells, and made the cancer cells resistant to bevacizumab treatment [140]. Several studies have investigated the role of autophagy-related genes in the context of colorectal cancer. Interestingly, BECN1 is reported to have a contrasting roles in colorectal cancer. The higher expression of BECN1, which was reported in 95 % of CRCs, was found to promote tumorigenesis and distant metastasis of colorectal carcinoma [141,142]. On the other hand, Koneri et al. demonstrated that the BECN1 gene inhibits tumor growth in colon cancer cells [143]. In another study, it was shown that high expression of the core autophagy gene ATG16L1 in colorectal tumors results in the suppression of anti-tumor immunity, and a poor clinical response to anti-PD-L1 therapy in KRAS-mutant tumors [144]. Salidroside, which is a bioactive compound found in the root of the *Rhodiola rosea* plant, was also reported to inhibit the growth of gastric cancer cells by the induction of autophagy and apoptosis through the PI3K/Akt/mTOR pathway (Table 2) [93]. Thus, the context-dependent use of chemotherapeutic drugs, which can modulate the autophagic flux in tumor cells, can provide a promising therapeutic potential in the treatment of colorectal cancer.

5.6. Prostate cancer

Prostate cancer, the most prevalent cancers in male's development and progression are influenced by a variety of cellular processes, such as autophagy [145]. The proliferation and survival rate of prostate cancer cells are among the primary effects of autophagy, that arises from the complex interaction with a variety of molecular pathways [146]. The majority of fatalities in patients with prostate cancer (PCa) are caused by castration-resistant prostate cancer (CRPC) [147], which is significantly influenced by the androgen receptor (AR) axis [148]. Lysine demethylase KDM4B, a key molecule in AR signalling and turnover plays a vital role in PC progression along with autophagy. The recent findings include the overexpression of KDM4B, resulting in the activation of Wnt/β-catenin signalling and autophagy which results in increased cancer progression [149]. The vital role of AR axis is further explained in another research based on SIRT7, a deacetylase whose depletion resulted in the reduced expression of autophagy-related genes like ATG4B and ATG4D, which are known to be regulated by AR. It was also observed that restoration of AR expression resulted in increased autophagy and prostate cancer progression [150]. Recent research on HnRNPL, an RNA binding protein was found to upregulate the expression of circCSPP1, a circular RNA, which then acts as a sponge for miR-520h, leading to increased EGR1 expression and subsequent induction of autophagy. The increased autophagy induced by the circCSPP1/miR-520h/EGR1 axis then led to enhanced proliferation, migration, and invasion of prostate cancer cells *in vitro* and accelerated tumor growth *in vivo* [151]. A micro-RNA-based recent research study showed that miR-99b directly binds to the 3′UTR of the mTOR gene and inhibits its expression, resulting in the induction of autophagy of PCa cells. The miR-99b was also found to inhibit the AR signalling pathway, which is known to promote cancer progression [152]. A related recent breakthrough was observed regarding AR signaling, which upregulates the DNM1L, a crucial component of the mitochondrial and peroxisomal fission machinery, which inhibits autophagy and promote proliferation in prostate cancer. Thus, autophagy plays a crucial role in both promoting and inhibiting the proliferation of prostate cancer cells, representing the complex influence on tumor dynamics [146].

The reduced expression of autophagy genes such as FIP200, ATG16L1, and GABARAPL1 in clinical cohorts regulating cancer metabolism [153], demonstrate poor prognosis in prostate cancer [154]. A metabolic hormone, FGF21, primarily produced in the liver and playing a major role in glucose and lipid metabolism, is found to be downregulated in prostate cancer tissues and cell lines. H. Dai et al. reported that FGF21 enhances autophagy by inhibiting PI3K–Akt–mTOR pathway, which contributes to tumor suppression [155]. Another study has identified the role of a lipid kinase, PIKfyve, targeted by ESK981, that blocks the autophagic flux in prostate cancer cells. This results in increased expression of CXCL10, recruiting T cells into the tumor microenvironment, and effectively converting "cold" tumors to "hot" tumors which is more susceptible to immune checkpoint blockade [156]. Novel research works based on nanodrugs are now done in parallel, linking autophagy with the immune system in prostate cancer. Recently a PDPA-cored nanodrug (PD-PSL1-CP) was developed that delivers anti-PD-L1 which inhibits autophagy. The nanodrug's tumor microenvironment pH-sensitive design allowed for the selective release of a PD-L1 and enhanced the PDPA uptake in cancer cells. PDPA blocked the autophagic flux by disturbing lysosomes, leading to increased MHC-I expression on cancer cells, which boosted their vulnerability to TNF-α and cytotoxic T lymphocytes (CTLs) [95].

Prostate cancer-related therapeutic research is currently undergoing in full swing. Recent research related to Apalutamide, an androgen receptor antagonist demonstrated that it induces autophagy in prostate cancer cells as shown by increased levels of autophagy markers like ATG5, Beclin 1, and LC3. However, autophagy appears to act as a pro-survival mechanism, potentially contributing to resistance against Apalutamide. When combined with autophagy inhibitors such as 3-methyladenine or chloroquine, apalutamide significantly enhanced the tumor cell death, suggesting that blocking autophagy can improve its therapeutic efficacy (Table 2) [96]. Another drug, Simvastatin (Table 2), was recently administered in prostate cancer, and it demonstrated a significant concentration-dependent growth inhibition effect on prostate cell lines. A notable enhancement in autophagy was detected in all cell lines subsequent to simvastatin treatment and its combination with rapamycin further induced autophagy and enhanced its inhibitory effects [97].

6. Autophagy: Converging aging and cancer

Extensive research has illuminated the intricate link between aging and cancer, revealing how the former fuels the latter's development. The role of autophagy is widely studied in regulating tumorigenesis at

different stages; however whether autophagy mediated aging process regulates the tumorigenesis still require further investigation. Autophagy during the later stages of tumor development, often promotes tumor growth by providing the essential raw materials and scavenging toxic molecules involved in abstaining tumorigenesis. Additionally, the aging of cells promotes proinflammatory environment, where it allows the cancer cells to emerge. Many studies have shown that autophagy and aging are highly convoluted, where autophagy is critically important in regulating hallmarks of aging.

A central paradigm of autophagy and aging in regulating cancer is that, the aging cells gradually experience lack of functional autophagy process, as ATG genes and other factors such as sirtuin decreases, which promotes favourable environment for tumor growth. One of the hallmarks of aging is decrease in heteroplasmy of mtDNA, in which mitophagy plays an important role in maintaining homogeneity of mtDNA. The mutations and deletions of mtDNA increases with age that results in increase in energy of mitochondrial output, increased ROS production that emerges the cancer growth [157]. Considering the complicated relationship of p53 and autophagy, p53 suppression and activation of autophagy has a crucial role in modulating cancer growth, as mutant p53 is involved in inhibiting the autophagy vesicle formation. Interestingly, the activity of p53 gradually decreases with the aging of the cells, suggesting crucial role of p53 at intersection of autophagy, aging and cancer [158].

In the following section, we discuss how autophagy regulates age-dependent cancer development, focusing on key cancer hallmarks, including metabolism, cellular stress (such as hypoxia), and epigenetic age as mentioned in Fig. 4.

i) Metabolism

Glucose metabolism is a critical process that is inherently linked to autophagy and plays a crucial role in both aging and cancer development [159]. Dysregulation of glucose metabolism or glycolysis can disrupt cellular homeostasis and contribute to various diseases, including cancer, neurodegenerative disorders, diabetes, and aging [160]. The switch in the glycolytic pathway to mitochondrial oxidation or vice-versa has been highly studied in the context of tumor progression [62] and aging in cells [161]. Cancer cells predominantly produce energy from glycolysis by a phenomenon known as the Warburg effect. Autophagy can further support this metabolic shift by providing recycled nutrients and maintaining mitochondrial integrity, even though mitochondrias are not the primary energy source in cancer cells. On the other hand, the increased mitophagy in the fibroblast mitigates mitochondrial dysfunction and leads to lactate production. This lactate, secreted by stromal cells, subsequently fuels the oxidative metabolism of cancer cells, a process known as the reverse Warburg effect, which is essential for tumor progression [62]. Given the versatility of the autophagy process, it is not surprising that under stress conditions, autophagy plays an important role in switching metabolic pathways essential for the growth of cancer cells. In 2020, Kawaguchi et al. reported that inhibition of glycolysis enhanced autophagy in cancer cells, promoting

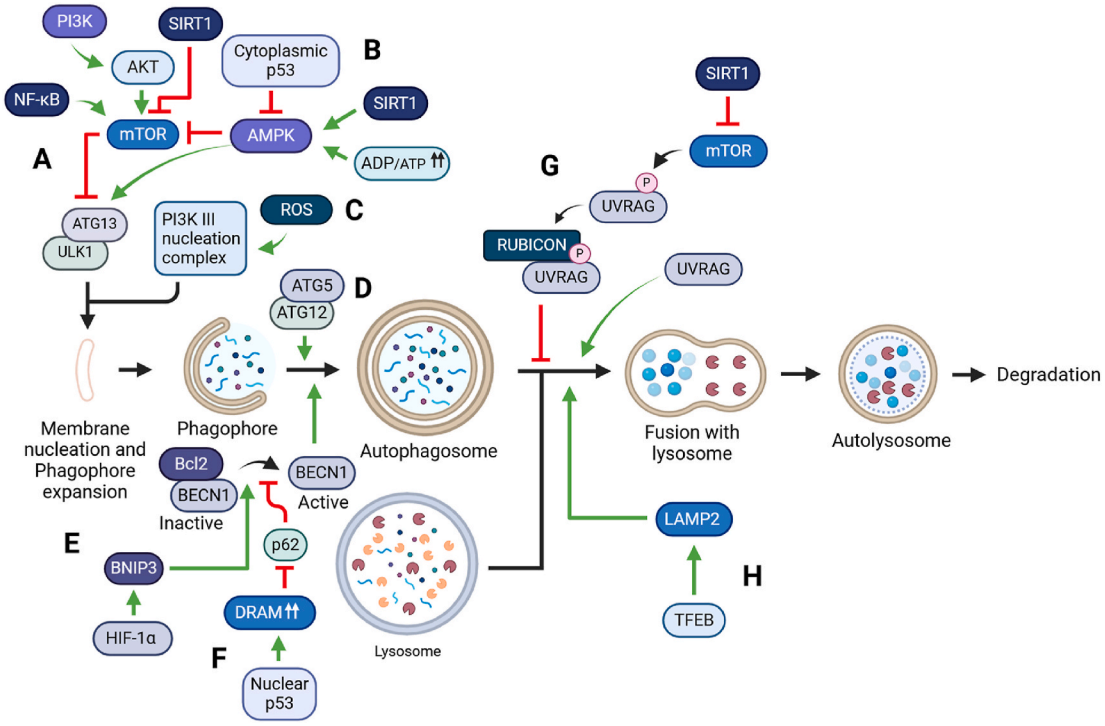

Fig. 4. Common pathways of cancer and aging regulate autophagy machinery. A. mTOR (mechanistic target of rapamycin) inhibits the ATG13/ULK1 complex, which is essential for phagophore formation. mTOR is in turn activated by NF-κB and AKT (which is activated by PI3K), and is inhibited by SIRT1 (Sirtuin 1) and AMPK (AMP-activated protein kinase). AMPK can also directly activate the ATG13/ULK1 complex to promote autophagy. **B.** cytoplasmic p53 has been reported to inhibit autophagy indirectly by suppressing AMPK activation, which consequently reduces the inhibition of mTOR, thereby dampening autophagy initiation. AMPK is activated by SIRT1 and by an increase in the level of ADP/ATP in the cell. **C.** An increase in the level of ROS in the cell can promote the formation of the PI3K III nucleation complex necessary for phagophore formation. **D.** The ATG5/ATG12 complex promotes autophagy by facilitating LC3 lipidation for autophagosome formation. **E.** Under stress conditions such as hypoxia, HIF-1α leads to the expression of BNIP3, which activates BECN1 by promoting the dissociation of BCL-2 from BECN1 by competing for BCL-2 binding, thus leading to autophagosome maturation. **F.** Nuclear p53, unlike cytoplasmic p53, promotes autophagy under certain stress conditions (such as DNA damage) by increasing the expression of DRAM (Damage-Regulated Autophagy Modulator); an increase in the expression of DRAM leads to the decrease in the level of p62, and thus p62 can no longer inhibit the activation of BECN1. **G.** UVRAG facilitates the fusion of autophagosome with lysosome. mTOR phosphorylates UVRAG, to which RUBICON binds, preventing UVRAG from carrying out its function, thus leading to autophagy inhibition. mTOR is inhibited by SIRT1. **H.** LAMP2 (Lysosomal Associated Membrane Protein 2) promotes autophagosome-lysosome fusion; LAMP2 expression is in turn upregulated by TFEB (Transcription Factor EB).

mitochondrial OXPHOS for ATP production essential for survivability [162]. Additionally, the combinatorial treatment of 2-DG (glycolysis inhibitor) and propranolol in a study by Laura Brohée et al. prevents prostate cancer cell proliferation due to the inhibition of autophagy, which would otherwise promote mitochondrial bioenergetics and the survivability of prostate cancer cells [163]. The impairment of mitochondrial activity and its clearance by autophagy are clear determinants of the longevity of cells. Mitochondrial function, including ATP synthesis, tends to decline with age, resulting in a spike in blood glucose levels after meals. Thereby, necessary physical activity, the intake of unprocessed food, and fasting maintain the autophagy process in the aging cells. Just like recently, Dellurusso et al. talked about the regenerative potential of HSCs due to adaptive fasting-induced autophagic activity in response to an increase in chronic inflammation with age. As in old-HSCs inflammation suppresses glycolysis through Socs3 mediated Akt/FoxO dependent signalling. However, transient autophagy induction via fasting normalizes glycolysis and feed oHSCs regenerative potential [164]. The question remains, however, as to whether age-related dysfunction in autophagic activity is more reliant on anaerobic glycolysis than oxidative metabolism. In 2016, Feng et al. reported the reciprocal changes in PEPCK-C and PK with age and associated metabolic pathways, including oxidative metabolism and anaerobic glycolysis, in C elegans. PEPCK-C promotes autophagy and ATP turnover with the help of AMPK, which gradually decreases with the aging of the cells. Due to a lack of clearance of dysfunctional mitochondria by autophagy, there is less oxidation of fats to produce ATP [165]. On the other hand, an increase in glycolytic flux and PK enzyme results in the pyruvate shunt to gluconeogenesis and lipogenesis, which is responsible for more fat deposition and obesity in mice and humans. The increased dependency on anaerobic glycolysis results in acidosis of cells, a glucose spike in the blood, suppressed insulin sensitivity [166], and low expression of sirtuins (due to low NAD+) [167], disrupting the homeostasis of the cells. These changes fortify the tumorigenesis and prevalence of diabetes with the early aging of the cells.

Overall, the metabolic regulation of autophagy plays a crucial role in influencing age-dependent tumor progression and maintaining cellular health during aging.

ii) Stress-Inducible autophagy

Hypoxic conditions develop in the local tissues when the demand for oxygen surpasses its supply, which often occurs during the progression of various diseases [168]. This imbalance activates few compensatory stress-adaptable processes, including autophagy.

The cells experiencing hypoxic conditions transduce the signal to the HIF pathway, which regulates more than 100 genes by binding to the hypoxia-responsive element within the promoter or enhancer region of hypoxia-responsive genes. The activated genes further regulate various biological processes such as glycolysis, angiogenesis, erythropoiesis, pH regulation, cancer metastasis, etc [168]. The development of hypoxic condition during aging and tumorigenesis activate several common autophagy genes such as sirtuin, AMPK, and NF-kB [169]. During hypoxia, the levels of mTOR and phosphorylated ULK1 (Ser 757) gradually decrease, which promotes autophagy, supporting tumorigenesis and age-related diseases [44]. Aging-associated reductions in ATPs and NAD + levels decrease SIRT1 activity, impairing mitochondrial biogenesis and leads to the accumulation of HIF1α through diminished pVHL levels [170,171]. The increased HIF1α in aging cells, or in SIRT1 knockout cells, activates the Mxi gene encoding c-Myc transcriptional repressor that affects mitochondrial biogenesis. This increased Mxi gene restricts the interaction between c-Myc and mitochondrial transcription factor A (TFAM), critical for replication, transcription, and maintenance of mitochondrial biogenesis [172]. SIRT1 mRNA transcription is also coupled with hypoxia by the FOXO3a pathway. In response to DNA damage, FOXO1 binds to the SIRT1 promoter and increases its transcription. Under stress conditions, SIRT1 deacetylases and transactivates FOXO 1 in an NAD + -dependent manner and promotes tumor progression with reduced expression of p53 and p21 [173]. AMPK, another key regulator in hypoxia, interacts with SIRT1 to modulate mitochondrial biogenesis via PGC1α [174]. Hypoxic conditions activate AMPK either by a high AMP: ATP ratio or indirectly by SIRT1-LKB1. In addition to hypoxic conditions other stress factors such as imbalanced pH and accumulated ROS are also responsible for the induction of autophagy. The induced autophagy further connects cancer treatment along with the underlying aging effects, however further research is still required to bridge the gap in understanding the connection between adaptive autophagy with age-dependent cancer treatment.

iii) Epigenetic Age and Biological Age

The interplay between external environmental factors and epigenetic modifications has brought significant attention to the concept of epigenetic age as a complement to the biological age in understanding the aging process. Chronological aging has long been associated with an increased risk of cancer, as well as molecular, cellular, and tissue-level aberrations influenced by genetic and environmental factors [175]. Among the epigenetic modifications, DNA methylation is a prominent epigenetic mark that contributes to deciphering the “epigenetic aging” process [176]. Various biomarkers have been identified that link the biological age to chronological age, and fewer studies have deciphered the role of autophagy in balancing the biological age with chronological age [177]. Autophagy has always been studied as a factor in slowing down aging [37]. Moreover, there is evidence that artificial maintenance of basal autophagy upon aging, for example, by overexpressing ATG5 in mice or Atg8a, Atg1 or SQSTM1 in fruit flies, or SQST-1 in nematodes, increases longevity in life [178]. Additionally, a knock-in-function mutation in *Becn1* results in disruption of inactivated Bcl2-BECN1 and perpetual activation of autophagy [179]. It appears that prolonged lifespan upon starvation is dependent on autophagy and is observed in autophagy-proficient animals. As it was evidently observed by Juhász et al. in D. melanogaster that lacks the core Atg7 complex pivotal for autophagy machinery, even upon starvation, does not have a prolonged lifespan [180]. The depletion of Atg7 and Becn1 in C. elegans abolished the effects of longevity even on the application of resveratrol or nutrient deficit conditions. Similarly, silencing SIRT1 expression in the nematode, which is required for starvation-induced autophagy, abrogated the extended lifespan of the worm [181].

The regulation of autophagy in enucleated cells underscores the dispensability of the nucleus for the autophagic process. Concurrently, studies by Beck and Hall, and other researchers reported mTOR mediated transcription of genes activated by autophagy stimuli [182,183]. However, Fullgrabe et al., in 2013 reported that induction of autophagy downregulates the histone acetyltransferase hMOF which is coupled with the reduction of H4K16ac and demonstrated that this histone modification regulated the outcome of autophagy [184].Recent study by Tang et al. unveils an mTOR signalling cascade that regulate m^6A methylation and autophagy. They reported that mTORC1 stabilize m6A methyltransferase complex (MTC) via activation of the chaperonin CCT complex and upregulate m^6A modification to promote the degradation of ATG transcripts [185]. The alterations in various epigenetic mechanisms in *C. elegans* [186] and *D. melanogaster* [187] are reported to impact longevity. Thereby, considering induction of autophagy and the epigenetic alteration as an outcome provides a potential therapeutic target for effective longevity. The H4K16 deacetylation is associated with induction of autophagy that downregulates autophagy-related genes and provides a negative regulatory feedback loop, becoming a key determinant of survival versus death response. H4K16 acetylation affects lifespan due to a decrease in H4K16 deacetylase Sir2, similarly, in D. melanogaster, a decrease in dSir2 blocks the calorie deficit autophagy induction-mediated extended lifespan. In mammalian cells, during starvation conditions, H3K9 methyltransferase G9a chromatin displacement leads to reductions in H3K9me3 levels and activation of

ATG genes [188].

EZH2 is a positive regulator of autophagy acquiring Polycom Repressive Complex 2 (PRC2) and is a H3K27 methyltransferase [189]. It downregulates TSC2, that elicits mTOR activation and inhibits autophagy. In D. melanogaster [190] and C. elegans [191], increased EZH2 promotes early life dietary restrictions and a shorter lifespan of the offspring. The ULK3-mediated activation of DNMT3a promotes methyltransferase activity [192]. However, longitudinal transcriptomic data available for murine lung tissues shows early neonatal starvation period resulted in decreased expression of *Map1lc3b while increase in Dnmt3a* expression levels [193].These studies indicated the role of epigenetic or posttranslational modifications of autophagy genes and their impacts on aging; however, several questions are still unresolved. Considering the vast role epigenetics play in harboring cancer cell survivability and death, i) how autophagy-mediated regulation of the epigenetic age impacts the survivability of cancer cells? and ii) whether epigenetic modifications on autophagy genes can promote aging instead of slowing it down? Understanding these intricate interactions could pave the way for novel strategies targeting autophagy and epigenetic mechanisms to modulate aging and cancer progression.

7. Therapeutics

Autophagy is a crucial cellular process involved in regulating various diseases, including cancer and aging, making it a therapeutically targetable pathway. The cascade of reactions during autophagosome formation provides opportunities to modulate autophagy and alter associated disease outcomes (Table 3). However, monitoring autophagosome formation is challenging due to the degradation of membrane-embedded components following the fusion of autophagosomes with lysosomes. Several drugs inhibit autophagy by blocking the fusion of autophagosomes and lysosomes, thereby maintaining the early stages of autophagy.

i) Chloroquine and Hydroxychloroquine

Chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) are FDA-approved drugs that impair autophagosome-lysosome fusion. These drugs are being evaluated in clinical trials as combinatorial agents with chemotherapeutic drugs [138].

Doeppner et al. observed that chloroquine administered in drinking water extended the lifespan of the middle-aged NMRI male mice while inhibiting the autophagy flux in the liver and heart tissue [196]. The low dose of chloroquine attenuates age-associated gene expression across tissue. CQ treatment enhances DNA damage clearance and rescues age-related metabolic shifts [197]. In the context of cancer, chloroquine's role has been studied mainly in sensitizing cancer cells against chemotherapeutic drugs and altering therapeutic strategies. The autophagy process in normal tissues maintains a slightly alkaline pH; however, due to the perpetual Warburg effect, the resultant lactic acid releases ample amounts of protons, causing elevated acidic pH. The CQ is the best approach to target the pH of cancer cells since it is an inhibitor of lysosomal autophagy that strengthens the antineoplastic immune response and interferes with key events, including cellular metabolism and gene regulation in the tumor microenvironment [213,194]. Among CQ analogs, HCQ is preferred due to its enhanced potency and minimum side effects. HCQ acts as a promising chemo-sensitizer and potential repurposed drug either as monotherapy or combinatorial therapy [214]. HCQ has not been studied for its effect on aging; considering its role in low blood glucose, elevating the pH of tissues, and maintaining cellular metabolism, it would be interesting to evaluate the role of HCQ on aging tissues at different dosages.

i) Bafilomycin

Bafilomycin A1 (BafA1) is essentially a lysosome inhibitor that displays cytotoxic effects in several types of cancer cells when present at high concentrations [209]. Yan et al. had studied the effect of bafilomycin treatment in hepatocellular carcinoma cells, induces caspase-dependent cell death along with impairing the autophagy flux of the cell, which was exhibited by higher LC3 conversion and

Table 3
Common therapeutic drugs targeting autophagy in cancer and aging treatment.

Drug	Mechanism in Cancer	Mechanism in Aging
Chloroquine	Inhibition of autophagy by preventing autophagosome and lysosome fusion Targeting pH in cancer cells by inhibiting lysosomal autophagy Strengthening anticancer immune response Interfering with cellular metabolism and gene regulation Sensitizing cancer cells towards chemotherapeutic drugs [194,195]	Inhibition of autophagic flux by preventing autophagosome and lysosome fusion [196] Decline in age-associated gene expression [197] Enhanced clearance of DNA damage Rescue of age-related metabolic shift [197]
Hydroxychloroquine	Inhibition of autophagy by preventing autophagosome and lysosome fusion Reduction of blood glucose level Elevating pH of tissues Maintenance of cellular metabolism [195,198]	
Rapamycin	Induction of autophagy by targeting PI3K/AKT/mTOR pathway to reduce cancer growth Promotion of apoptosis [199,200]	Inhibition of mTOR, Autophagy induction by PGC1-α and ATG13 proteins, Decrease in ROS production [201]
Resveratrol	Antioxidant and anti-inflammatory effect Induction of protective autophagy by increasing mRNA expression of NGFR-AMPK-mTOR pathway Sensitizing cancer cells towards chemotherapeutic drugs [202]	Antioxidant and anti-inflammatory effect [181] Induction of sirtuin-dependent autophagy [203] Regulation of mitochondrial function [203]
Metformin	Reduction of blood glucose level by altering glucose metabolism Induction of autophagy by the inhibition of mTORC1 [204] Activation of AMPK and downregulation of c-MYC [205]	Activation of AMPK and LKB1 [206] Improving insulin sensitivity [207] Promote cellular repair [207] Antioxidant and anti-inflammatory action [207] Modulation of hepatic stress by the activation of APMK and CAMKII-mediated signalling and the inhibition of ERK [208] Skeletal mass maintenance by the induction of Akt phosphorylation and activation [208]
Bafilomycin	Lysosome inhibition [209] Impairment of autophagic flux [210] Induction of caspase-dependent cell death [210] Inhibition of cancer cell proliferation [211]	
3-methyladenine	Inhibition of autophagy by disrupting PI3K activity, preventing autophagosome and autophagic vacuole formation [212]	

p62/SQSTM1 levels [210]. BafA1 is also known to inhibit autophagy in osteosarcoma cells, leading to the induction of apoptosis along with the inhibition of cancer cell proliferation [211].

ii) Rapamycin

Rapamycin, also called sirolimus, is a potent inhibitor of the mechanistic target of rapamycin (mTOR), which is used as an anti-aging drug, drug-eluting coronary stents, and anti-cancer drug, primarily due to its ability to induce autophagy, which is involved in enhancing the lifespan of the tissues [215]. According to V Martínez-Cisuelo, rapamycin treatment in mice has a qualitative effect on complex I of mitochondria by decreasing the ROS production. Furthermore, rapamycin treatment decreased the amount of RAPTOR, on the other hand, increased the amount of PGC1-α and ATG13 proteins, promoting autophagy that scavenges the final form of damage accumulated with age [201]. Rapamycin treatment is also accepted for its anti-proliferative properties in oral, lung, breast, and cervical cancer [215]. Rapamycin majorly induces autophagy by targeting the PI3K/AKT/mTOR pathway to alleviate cancer growth; however, signals transmitted from the upstream pathway still provide survivability and proliferation. Neslihan Pinar Ozates et al. reported the combinatorial treatment of rapamycin with AZD3463, an anti-cancer agent that inhibits ALK/IGF1R, results in increased expression of CDKN1B, PTEN, FOXO3, and APC genes. Additionally, it promoted apoptosis, autophagy and cell population in the G0/G1 stage in MCF7 cells [199]. Interestingly, autophagy duality of action can be understood by targeting autophagy with a synergistic combination of CQ and Rapamycin. CQ targets proliferation by inhibiting autophagy and sensitizing chemotherapeutic drugs, whereas rapamycin targets proliferation by promoting autophagy. However, the combination of CQ and Rapamycin acts as autophagy inhibitors by overproducing autophagosomes in liposarcoma, proving it to be a new paradigm for treating sarcoma. Dietary habits majorly impact the induction of autophagy in the cells [200].

iii) Resveratrol

Reservatrol is found in various foods such as grapes, red wine, and blueberries, and it has anti-inflammatory, antioxidant, anticancer, and anti-aging effects [216]. Morselli E et al. reported Resveratrol induced sirtuin-dependent autophagy that promotes longevity in C elegans [181]. Further, Sugiyama M et al. mentioned the role of Resveratrol in regulating mitochondrial function and Sirt1-mediated autophagy in human oocytes [203]. In the context of cancer, Resveratrol induces protective autophagy by increasing mRNA expression of the NGFR-AMPK-mTOR pathway in non-small-cell lung cancer A549 cells [202]. Unlike CQ, resveratrol sensitizes cancer cells towards chemotherapeutic drugs by inducing autophagy instead of inhibiting it.

iv) Metformin

Metformin is widely used medication approved by the FDA in 1994, which is prescribed to patients with type 2 diabetes mellitus (T2DM). It acts by altering the glucose metabolism in the cells. Both aging and cancer are linked to the glucose metabolism pathway, making metformin considerably effective on aging and cancer. According to a study by Decensi and his team, patients taking metformin showed a 31 % decrease in the relative cancer risk compared to patients taking other antidiabetic drugs [217]. Metformin mainly works by inhibiting the mTORC1 in the cells [204] which results in the induction of autophagy and the subsequent tumorigenesis prevention, which was shown in a work conducted by De Santi et al. [218]. Blandino and his team also reported Metformin to activate AMPK, that downregulates c-MYC, in breast cancer cells [205]. Additionally, the activation of AMPK and AMPK-activating kinase LKB1 by Metformin has also shown to increase average lifespan by 40 % in *C elegans* [206]. Anisimov and his team showed treatment of metformin increased lifespan of female HER-2/neu transgenic mice which were short-lived and cancer-prone [219]. Metformin includes several beneficial properties including improved insulin sensitivity, anti-aging, antioxidant and anti-inflammatory activities [207]. Therefore, this drug has therapeutic potential that simultaneously targets aging and cancer along with influencing autophagy mechanism in the cells.

In conclusion, the dual role of autophagy in promoting cellular survival and inducing cell death underscores its complexity as a therapeutic target in aging and cancer. While drugs like chloroquine, rapamycin, and metformin highlight the potential of modulating autophagy for improved lifespan and cancer treatment, their context-specific effects necessitate a nuanced approach. Exploring synergistic drug combinations and understanding the molecular mechanisms governing autophagy will pave the way for innovative therapies that balance cellular homeostasis and disease mitigation effectively.

8. Conclusion

The review has covered various aspects of autophagy intersecting the cancer and ageing process, however there are still open questions that needs to be answered. i) Does autophagy deregulation induce aging and tumorigenesis in the cells, or do these two processes exploit autophagy for their progression? ii) Is autophagy targeting drugs enough to target aging and tumorigenesis simultaneously in the cells? iii) Does the effectiveness of autophagy play a role in influencing or deciphering the biological age, epigenetic age, etc.?

CRediT authorship contribution statement

Anchala Pandey: Writing – review & editing, Writing – original draft. **Ankit Goswami:** Writing – review & editing, Writing – original draft. **B. Jithin:** Writing – review & editing, Writing – original draft. **Sanjeev Shukla:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

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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References

[1] C.M. Anderson, K.F. Macleod, Autophagy and cancer cell metabolism, in: International Review of Cell and Molecular Biology, Elsevier, 2019, pp. 145–190, https://doi.org/10.1016/bs.ircmb.2019.06.002.
[2] J. Nah, J. Yuan, Y.-K. Jung, Autophagy in neurodegenerative diseases: from mechanism to therapeutic approach, Mol. Cells 38 (2015) 381–389, https://doi.org/10.14348/molcells.2015.0034.
[3] Y. Feng, D. He, Z. Yao, D.J. Klionsky, The machinery of macroautophagy, Cell Res. 24 (2014) 24–41, https://doi.org/10.1038/cr.2013.168.
[4] Y. Ohsumi, Molecular mechanism of autophagy in yeast, Saccharomyces cerevisiae, Philos. Trans. R. Soc. Lond. B Biol. Sci. 354 (1999) 1577–1580, https://doi.org/10.1098/rstb.1999.0501. ; discussion 1580-1581.
[5] T. Sekito, T. Kawamata, R. Ichikawa, K. Suzuki, Y. Ohsumi, Atg17 recruits Atg9 to organize the pre-autophagosomal structure, Genes Cells 14 (2009) 525–538, https://doi.org/10.1111/j.1365-2443.2009.01299.x.
[6] I. Tanida, T. Ueno, E. Kominami, LC3 and autophagy, Methods Mol. Biol. 445 (2008) 77–88, https://doi.org/10.1007/978-1-59745-157-4_4.
[7] T. Hanada, N.N. Noda, Y. Satomi, Y. Ichimura, Y. Fujioka, T. Takao, F. Inagaki, Y. Ohsumi, The Atg12-Atg5 conjugate has a novel E3-like activity for protein lipidation in autophagy, J. Biol. Chem. 282 (2007) 37298–37302, https://doi.org/10.1074/jbc.C700195200.

[8] H. Cheong, C. Lu, T. Lindsten, C.B. Thompson, Therapeutic targets in cancer cell metabolism and autophagy, Nat. Biotechnol. 30 (2012) 671–678, https://doi.org/10.1038/nbt.2285.
[9] C. López-Otín, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, Hallmarks of aging: an expanding universe, Cell 186 (2023) 243–278, https://doi.org/10.1016/j.cell.2022.11.001.
[10] H. Wang, J. Liu, G. Xia, S. Lei, X. Huang, X. Huang, Survival of pancreatic cancer patients is negatively correlated with age at diagnosis: a population-based retrospective study, Sci. Rep. 10 (2020) 7048, https://doi.org/10.1038/s41598-020-64068-3.
[11] C.D. Llewellyn, K. Linklater, J. Bell, N.W. Johnson, S. Warnakulasuriya, An analysis of risk factors for oral cancer in young people: a case-control study, Oral Oncol. 40 (2004) 304–313, https://doi.org/10.1016/j.oraloncology.2003.08.015.
[12] C. López-Otín, F. Pietrocola, D. Roiz-Valle, L. Galluzzi, G. Kroemer, Meta-hallmarks of aging and cancer, Cell Metab. 35 (2023) 12–35, https://doi.org/10.1016/j.cmet.2022.11.001.
[13] Y. Teng, D.Q. Huang, R.X. Li, C. Yi, Y.Q. Zhan, Association between telomere length and risk of lung cancer in an asian population: a mendelian randomization study, World J. Oncol. 14 (2023) 277–284, https://doi.org/10.4021/wjon.v14i4.1624.
[14] N.J. Robinson, W.P. Schiemann, Telomerase in cancer: function, regulation, and clinical translation, Cancers 14 (2022) 808, https://doi.org/10.3390/cancers14030808.
[15] R.T. Calado, J.A. Regal, M. Hills, W.T. Yewdell, L.F. Dalmazzo, M.A. Zago, P. M. Lansdorp, D. Hogge, S.J. Chanock, E.H. Estey, R.P. Falcão, N.S. Young, Constitutional hypomorphic telomerase mutations in patients with acute myeloid leukemia, Proc. Natl. Acad. Sci. USA 106 (2009) 1187–1192, https://doi.org/10.1073/pnas.0807057106.
[16] X. Zhu, W. Han, W. Xue, Y. Zou, C. Xie, J. Du, G. Jin, The association between telomere length and cancer risk in population studies, Sci. Rep. 6 (2016) 22243, https://doi.org/10.1038/srep22243.
[17] C. Franceschi, P. Garagnani, P. Parini, C. Giuliani, A. Santoro, Inflammaging: a new immune–metabolic viewpoint for age-related diseases, Nat. Rev. Endocrinol. 14 (2018) 576–590, https://doi.org/10.1038/s41574-018-0059-4.
[18] M.L. Fishel, M.R. Kelley, The DNA base excision repair protein Ape1/Ref-1 as a therapeutic and chemopreventive target, Mol. Aspect. Med. 28 (2007) 375–395, https://doi.org/10.1016/j.mam.2007.04.005.
[19] M. Li, X. Yang, X. Lu, N. Dai, S. Zhang, Y. Cheng, L. Zhang, Y. Yang, Y. Liu, Z. Yang, D. Wang, D.M. Wilson, APE1 deficiency promotes cellular senescence and premature aging features, Nucleic Acids Res. 46 (2018) 5664–5677, https://doi.org/10.1093/nar/gky326.
[20] C. Xia, Q. Meng, L.-Z. Liu, Y. Rojanasakul, X.-R. Wang, B.-H. Jiang, Reactive oxygen species regulate angiogenesis and tumor growth through vascular endothelial growth factor, Cancer Res. 67 (2007) 10823–10830, https://doi.org/10.1158/0008-5472.CAN-07-0783.
[21] J. Campisi, L. Robert, Cell senescence: role in aging and age-related diseases, Interdiscipl. Top Gerontol. 39 (2014) 45–61, https://doi.org/10.1159/000358899.
[22] G. Nelson, O. Kucheryavenko, J. Wordsworth, T. von Zglinicki, The senescent bystander effect is caused by ROS-activated NF-κB signalling, Mech. Ageing Dev. 170 (2018) 30–36, https://doi.org/10.1016/j.mad.2017.08.005.
[23] M.F. Fraga, R. Agrelo, M. Esteller, Cross-talk between aging and cancer, Ann. N. Y. Acad. Sci. 1100 (2007) 60–74, https://doi.org/10.1196/annals.1395.005.
[24] B. Kwabi-Addo, W. Chung, L. Shen, M. Ittmann, T. Wheeler, J. Jelinek, J.-P.J. Issa, Age-related DNA methylation changes in normal human prostate tissues, Clin. Cancer Res. 13 (2007) 3796–3802, https://doi.org/10.1158/1078-0432.CCR-07-0085.
[25] S.E. Goelz, B. Vogelstein, S.R. Hamilton, A.P. Feinberg, Hypomethylation of DNA from benign and malignant human colon neoplasms, Science 228 (1985) 187–190, https://doi.org/10.1126/science.2579435.
[26] V.L. Wilson, P.A. Jones, DNA methylation decreases in aging but not in immortal cells, Science 220 (1983) 1055–1057, https://doi.org/10.1126/science.6844925.
[27] R.F. Pérez, J.R. Tejedor, G.F. Bayón, A.F. Fernández, M.F. Fraga, Distinct chromatin signatures of DNA hypomethylation in aging and cancer, Aging Cell 17 (2018) e12744, https://doi.org/10.1111/acel.12744.
[28] M.S. Bonkowski, D.A. Sinclair, Slowing ageing by design: the rise of NAD+ and sirtuin-activating compounds, Nat. Rev. Mol. Cell Biol. 17 (2016) 679–690, https://doi.org/10.1038/nrm.2016.93.
[29] E. Michishita, R.A. McCord, E. Berber, M. Kioi, H. Padilla-Nash, M. Damian, P. Cheung, R. Kusumoto, T.L.A. Kawahara, J.C. Barrett, H.Y. Chang, V.A. Bohr, T. Ried, O. Gozani, K.F. Chua, SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin, Nature 452 (2008) 492–496, https://doi.org/10.1038/nature06736.
[30] V. Byles, L. Zhu, J. Lovaas, L. Chmilewski, J. Wang, D. Faller, Y. Dai, SIRT1 induces EMT by cooperating with EMT transcription factors and enhances prostate cancer cell migration and metastasis, Oncogene 31 (2012) 4619–4629, https://doi.org/10.1038/onc.2011.612.
[31] R.J. Shaw, M. Kosmatka, N. Bardeesy, R.L. Hurley, L.A. Witters, R.A. DePinho, L. C. Cantley, The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress, Proc. Natl. Acad. Sci. USA 101 (2004) 3329–3335, https://doi.org/10.1073/pnas.0308061100.
[32] C.D. Young, L.J. Zimmerman, D. Hoshino, L. Formisano, A.B. Hanker, M.L. Gatza, M.M. Morrison, P.D. Moore, C.A. Whitwell, B. Dave, T. Stricker, N.E. Bhola, G. O. Silva, P. Patel, D.M. Brantley-Sieders, M. Levin, M. Horiates, N.A. Palma, K. Wang, P.J. Stephens, C.M. Perou, A.M. Weaver, J.A. O'Shaughnessy, J. C. Chang, B.H. Park, D.C. Liebler, R.S. Cook, C.L. Arteaga, Activating *PIK3CA* mutations induce an epidermal growth factor receptor (EGFR)/Extracellular signal-regulated kinase (ERK) paracrine signaling Axis in basal-like breast cancer, Mol. Cell. Proteomics 14 (2015) 1959–1976, https://doi.org/10.1074/mcp.M115.049783.
[33] L. Lagopoulos, R. Stalder, The influence of food intake on the development of diethylnitrosamine-induced liver tumours in mice, Carcinogenesis 8 (1987) 33–37, https://doi.org/10.1093/carcin/8.1.33.
[34] N. Pavlidis, G. Stanta, R.A. Audisio, Cancer prevalence and mortality in centenarians: a systematic review, Crit. Rev. Oncol. Hematol. 83 (2012) 145–152, https://doi.org/10.1016/j.critrevonc.2011.09.007.
[35] L. Zitvogel, M. Ayyoub, B. Routy, G. Kroemer, Microbiome and anticancer immunosurveillance, Cell 165 (2016) 276–287, https://doi.org/10.1016/j.cell.2016.03.001.
[36] R.J. Knippel, J.L. Drewes, C.L. Sears, The cancer microbiome: recent highlights and knowledge gaps, Cancer Discov. 11 (2021) 2378–2395, https://doi.org/10.1158/2159-8290.CD-21-0324.
[37] S. Kaushik, I. Tasset, E. Arias, O. Pampliega, E. Wong, M. Martinez-Vicente, A. M. Cuervo, Autophagy and the hallmarks of aging, Ageing Res. Rev. 72 (2021) 101468, https://doi.org/10.1016/j.arr.2021.101468.
[38] G.Y. Liu, D.M. Sabatini, mTOR at the nexus of nutrition, growth, ageing and disease, Nat. Rev. Mol. Cell Biol. 21 (2020) 183, https://doi.org/10.1038/s41580-019-0199-y.
[39] S. Alers, A.S. Löffler, S. Wesselborg, B. Stork, Role of AMPK-mTOR-ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks, Mol. Cell Biol. 32 (2012) 2, https://doi.org/10.1128/MCB.06159-11.
[40] Y.-M. Kim, J.-M. Park, D. Grunwald, D.-H. Kim, An expanded role for mTORC1 in autophagy, Mol Cell Oncol 3 (2016) e1010958, https://doi.org/10.1080/23723556.2015.1010958.
[41] K. Schmeisser, J.A. Parker, Pleiotropic effects of mTOR and autophagy during development and aging, Front. Cell Dev. Biol. 7 (2019) 192, https://doi.org/10.3389/fcell.2019.00192.
[42] Y. Wang, Z. Liu, S. Shu, J. Cai, C. Tang, Z. Dong, AMPK/mTOR signaling in autophagy regulation during cisplatin-induced acute kidney injury, Front. Physiol. 11 (2020), https://doi.org/10.3389/fphys.2020.619730.
[43] M. Holczer, B. Hajdú, T. Lőrincz, A. Szarka, G. Bánhegyi, O. Kapuy, Fine-tuning of AMPK–ULK1–mTORC1 regulatory triangle is crucial for autophagy oscillation, Sci. Rep. 10 (2020) 17803, https://doi.org/10.1038/s41598-020-75030-8.
[44] J. Kim, M. Kundu, B. Viollet, K.-L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, Nat. Cell Biol. 13 (2011) 132–141, https://doi.org/10.1038/ncb2152.
[45] D.-H. Kim, Contrasting views on the role of AMPK in autophagy, Bioessays 46 (2024) 2300211, https://doi.org/10.1002/bies.202300211.
[46] M. Ulgherait, A. Rana, M. Rera, J. Graniel, D.W. Walker, AMPK modulates tissue and organismal aging in a cell-non-autonomous manner, Cell Rep. 8 (2014) 1767–1780, https://doi.org/10.1016/j.celrep.2014.08.006.
[47] Y. He, Y. Fan, X. Ahmadpoor, Y. Wang, Z.A. Li, W. Zhu, H. Lin, Targeting lysosomal quality control as a therapeutic strategy against aging and diseases, Med. Res. Rev. 44 (2024) 2472–2509, https://doi.org/10.1002/med.22047.
[48] Y. Sun, M. Li, D. Zhao, X. Li, C. Yang, X. Wang, Lysosome activity is modulated by multiple longevity pathways and is important for lifespan extension in C. elegans, Elife 9 (2020) e55745, https://doi.org/10.7554/eLife.55745.
[49] R. Venz, T. Pekec, I. Katic, R. Ciosk, C.Y. Ewald, End-of-life targeted degradation of DAF-2 insulin/IGF-1 receptor promotes longevity free from growth-related pathologies, Elife 10 (2021) e71335, https://doi.org/10.7554/eLife.71335.
[50] L. Zhang, P. Yang, J. Chen, Z. Chen, Z. Liu, G. Feng, F. Sha, Z. Li, Z. Xu, Y. Huang, X. Shi, X. Li, J. Cui, C. Zhang, P. Fan, L. Cui, Y. Shen, G. Zhou, H. Jing, S. Ma, CD44 connects autophagy decline and ageing in the vascular endothelium, Nat. Commun. 14 (2023) 5524, https://doi.org/10.1038/s41467-023-41346-y.
[51] A. Simonsen, R.C. Cumming, A. Brech, P. Isakson, D.R. Schubert, K.D. Finley, Promoting basal levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult Drosophila, Autophagy 4 (2008) 176–184, https://doi.org/10.4161/auto.5269.
[52] Y. Yu, L. Feng, J. Li, X. Lan, L. A, X. Lv, M. Zhang, L. Chen, The alteration of autophagy and apoptosis in the hippocampus of rats with natural aging-dependent cognitive deficits, Behav. Brain Res. 334 (2017) 155–162, https://doi.org/10.1016/j.bbr.2017.07.003.
[53] M.M. Lipinski, B. Zheng, T. Lu, Z. Yan, B.F. Py, A. Ng, R.J. Xavier, C. Li, B. A. Yankner, C.R. Scherzer, J. Yuan, Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 14164–14169, https://doi.org/10.1073/pnas.1009485107.
[54] J.-O. Pyo, S.-M. Yoo, H.-H. Ahn, J. Nah, S.-H. Hong, T.-I. Kam, S. Jung, Y.-K. Jung, Overexpression of Atg5 in mice activates autophagy and extends lifespan, Nat. Commun. 4 (2013) 2300, https://doi.org/10.1038/ncomms3300.
[55] C. Wang, M. Haas, S.K. Yeo, S. Sebti, Á.F. Fernández, Z. Zou, B. Levine, J.-L. Guan, Enhanced autophagy in Becn1F121A/F121A knockin mice counteracts aging-related neural stem cell exhaustion and dysfunction, Autophagy 18 (2021) 409, https://doi.org/10.1080/15548627.2021.1936358.
[56] M.R. Chaudhary, S. Chaudhary, Y. Sharma, T.A. Singh, A.K. Mishra, S. Sharma, M.M. Mehdi, Aging, oxidative stress and degenerative diseases: mechanisms, complications and emerging therapeutic strategies, Biogerontology 24 (2023) 609–662, https://doi.org/10.1007/s10522-023-10050-1.
[57] S. Demirbag Sarikaya, H. Cakir, D. Gozuacik, Y. Akkoc, Crosstalk between autophagy and DNA repair systems, Turkish J. Biol. 45 (2021) 235, https://doi.org/10.3906/biy-2103-51.

[58] V. Karantza-Wadsworth, S. Patel, O. Kravchuk, G. Chen, R. Mathew, S. Jin, E. White, Autophagy mitigates metabolic stress and genome damage in mammary tumorigenesis, Gene Dev. 21 (2007) 1621, https://doi.org/10.1101/gad.1565707.

[59] D.E. Butler, C. Marlein, H.F. Walker, F.M. Frame, V.M. Mann, M.S. Simms, B. R. Davies, A.T. Collins, N.J. Maitland, Inhibition of the PI3K/AKT/mTOR pathway activates autophagy and compensatory Ras/Raf/MEK/ERK signalling in prostate cancer, Oncotarget 8 (2017) 56698–56713, https://doi.org/10.18632/oncotarget.18082.

[60] R. Mathew, C.M. Karp, B. Beaudoin, N. Vuong, G. Chen, H.-Y. Chen, K. Bray, A. Reddy, G. Bhanot, C. Gelinas, R.S. Dipaola, V. Karantza-Wadsworth, E. White, Autophagy suppresses tumorigenesis through elimination of p62, Cell 137 (2009) 1062–1075, https://doi.org/10.1016/j.cell.2009.03.048.

[61] K. Degenhardt, R. Mathew, B. Beaudoin, K. Bray, D. Anderson, G. Chen, C. Mukherjee, Y. Shi, C. Gélinas, Y. Fan, D.A. Nelson, S. Jin, E. White, Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis, Cancer Cell 10 (2006) 51–64, https://doi.org/10.1016/j.ccr.2006.06.001.

[62] A. Pandey, P. Yadav, S. Shukla, Unfolding the role of autophagy in the cancer metabolism, Biochem Biophys Rep 28 (2021) 101158, https://doi.org/10.1016/j.bbrep.2021.101158.

[63] D.A. Gillespie, K.M. Ryan, Autophagy is critically required for DNA repair by homologous recombination, Mol Cell Oncol 3 (2015) e1030538, https://doi.org/10.1080/23723556.2015.1030538.

[64] L. Duan, R.E. Perez, B. Davaadelger, E.N. Dedkova, L.A. Blatter, C.G. Maki, p53-regulated autophagy is controlled by glycolysis and determines cell fate, Oncotarget 6 (2015) 23135–23156, https://doi.org/10.18632/oncotarget.5218.

[65] S. Huang, M. Xu, L. Liu, J. Yang, H. Wang, C. Wan, W. Deng, Q. Tang, Autophagy is involved in the protective effect of p21 on LPS-induced cardiac dysfunction, Cell Death Dis. 11 (2020) 554, https://doi.org/10.1038/s41419-020-02765-7.

[66] K. Zheng, Z. He, K. Kitazato, Y. Wang, Selective autophagy regulates cell cycle in cancer therapy, Theranostics 9 (2019) 104–125, https://doi.org/10.7150/thno.30308.

[67] P. Kuballa, W.M. Nolte, A.B. Castoreno, R.J. Xavier, Autophagy and the immune system, Annu. Rev. Immunol. 30 (2012) 611–646, https://doi.org/10.1146/annurev-immunol-020711-074948.

[68] L. Mele, V. Del Vecchio, D. Liccardo, C. Prisco, M. Schwerdtfeger, N. Robinson, V. Desiderio, V. Tirino, G. Papaccio, M. La Noce, The role of autophagy in resistance to targeted therapies, Cancer Treat Rev. 88 (2020) 102043, https://doi.org/10.1016/j.ctrv.2020.102043.

[69] Z.J. Yang, C.E. Chee, S. Huang, F.A. Sinicrope, The role of autophagy in cancer: therapeutic implications, Mol. Cancer Therapeut. 10 (2011) 1533–1541, https://doi.org/10.1158/1535-7163.MCT-11-0047.

[70] R. Chavez-Dominguez, M. Perez-Medina, J.S. Lopez-Gonzalez, M. Galicia-Velasco, D. Aguilar-Cazares, The double-edge sword of autophagy in cancer: from tumor suppression to pro-tumor activity, Front. Oncol. 10 (2020) 578418, https://doi.org/10.3389/fonc.2020.578418.

[71] M.B. Schaaf, D. Houbaert, O. Meçe, P. Agostinis, Autophagy in endothelial cells and tumor angiogenesis, Cell Death Differ. 26 (2019) 665–679, https://doi.org/10.1038/s41418-019-0287-8.

[72] B. Kardideh, Z. Samimi, F. Norooznezhad, S. Kiani, K. Mansouri, Autophagy, cancer and angiogenesis: where is the link? Cell Biosci. 9 (2019) 65, https://doi.org/10.1186/s13578-019-0327-6.

[73] E.E. Mowers, M.N. Sharifi, K.F. Macleod, Autophagy in cancer metastasis, Oncogene 36 (2017) 1619–1630, https://doi.org/10.1038/onc.2016.333.

[74] C. Fung, R. Lock, S. Gao, E. Salas, J. Debnath, Induction of autophagy during extracellular matrix detachment promotes cell survival, Mol. Biol. Cell 19 (2008) 797–806, https://doi.org/10.1091/mbc.E07-10-1092.

[75] S.O. Bustos, F. Antunes, M.C. Rangel, R. Chammas, Emerging autophagy functions shape the tumor microenvironment and play a role in cancer progression - implications for cancer therapy, Front. Oncol. 10 (2020) 606436, https://doi.org/10.3389/fonc.2020.606436.

[76] E.E. Mowers, M.N. Sharifi, K.F. Macleod, Functions of autophagy in the tumor microenvironment and cancer metastasis, FEBS J. 285 (2018) 1751–1766, https://doi.org/10.1111/febs.14388.

[77] A.M. Strohecker, J.Y. Guo, G. Karsli-Uzunbas, S.M. Price, G.J. Chen, R. Mathew, M. McMahon, E. White, Autophagy sustains mitochondrial glutamine metabolism and growth of BrafV600E-driven lung tumors, Cancer Discov. 3 (2013) 1272–1285, https://doi.org/10.1158/2159-8290.CD-13-0397.

[78] M. Catalano, G. D'Alessandro, F. Lepore, M. Corazzari, S. Caldarola, C. Valacca, F. Faienza, V. Esposito, C. Limatola, F. Cecconi, S. Di Bartolomeo, Autophagy induction impairs migration and invasion by reversing EMT in glioblastoma cells, Mol. Oncol. 9 (2015) 1612–1625, https://doi.org/10.1016/j.molonc.2015.04.016.

[79] C. Fung, R. Lock, S. Gao, E. Salas, J. Debnath, Induction of autophagy during extracellular matrix detachment promotes cell survival, Mol. Biol. Cell 19 (2008) 797–806, https://doi.org/10.1091/mbc.e07-10-1092.

[80] I. Akalay, B. Janji, M. Hasmim, M.Z. Noman, F. André, P. De Cremoux, P. Bertheau, C. Badoual, P. Vielh, A.K. Larsen, M. Sabbah, T.Z. Tan, J.H. Keira, N. T. Ying Hung, J.P. Thiery, F. Mami-Chouaib, S. Chouaib, Epithelial-to-Mesenchymal transition and autophagy induction in breast carcinoma promote escape from T-cell–mediated lysis, Cancer Res. 73 (2013) 2418–2427, https://doi.org/10.1158/0008-5472.CAN-12-2432.

[81] K. Chaitanya Thandra, A. Barsouk, K. Saginala, J. Sukumar Aluru, A. Barsouk, Epidemiology of Lung Cancer, vol. 25, 2021, pp. 45–52, https://doi.org/10.5114/wo.2021.103829. Wo.

[82] A. Arif, M.B. Khawar, R. Mehmood, M.H. Abbasi, N. Sheikh, Dichotomous role of autophagy in cancer, Asian Biomed. 16 (2022) 111–120, https://doi.org/10.2478/abm-2022-0014.

[83] J.R. Molina, P. Yang, S.D. Cassivi, S.E. Schild, A.A. Adjei, Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship, Mayo Clin. Proc. 83 (2008) 584–594, https://doi.org/10.4065/83.5.584.

[84] S.-J. Jeon, J.-H. Ahn, D. Halder, H.-S. Cho, J.-H. Lim, S.Y. Jun, J.-J. Lee, J.-Y. Yoon, M.-H. Choi, C.-R. Jung, J.-M. Kim, N.-S. Kim, TIPRL potentiates survival of lung cancer by inducing autophagy through the eIF2α-ATF4 pathway, Cell Death Dis. 10 (2019) 959, https://doi.org/10.1038/s41419-019-2190-0.

[85] Q. Wang, Q. Zhang, X. Wang, H. Luo, T. Du, L. Wu, M. Tan, Y. Chen, X. Wu, S. Sun, Z. Liu, Y. Xie, W. Yuan, TGM2-Mediated autophagy contributes to the radio-resistance of non-small cell lung cancer stem-like cells, Biomedicines 12 (2024) 2231, https://doi.org/10.3390/biomedicines12102231.

[86] X. Luo, J. Wang, R. Wang, J. Lian, M. Guo, H. Zhou, M. Zhang, Z. Yang, X. Li, X. He, X. Bi, SLL-1A-16 suppresses proliferation and induces autophagy in non-small-cell lung cancer cells *via* the AKT/mTOR signaling pathway, RSC Med. Chem. 15 (2024) 3460–3468, https://doi.org/10.1039/D4MD00405A.

[87] T. Liu, Y. Li, J. Sun, G. Tian, Z. Shi, Gitogenin suppresses lung cancer progression by inducing apoptosis and autophagy initiation through the activation of AMPK signaling, Int. Immunopharmacol. 111 (2022) 108806, https://doi.org/10.1016/j.intimp.2022.108806.

[88] M. Hashemi, M.D.A. Paskeh, S. Orouei, P. Abbasi, R. Khorrami, A. Dehghanpour, N. Esmaeili, A. Ghahremanzade, M.A. Zandieh, M. Peymani, S. Salimimoghadam, M. Rashidi, A. Taheriazam, M. Entezari, K. Hushmandi, Towards dual function of autophagy in breast cancer: a potent regulator of tumor progression and therapy response, Biomed. Pharmacother. 161 (2023) 114546, https://doi.org/10.1016/j.biopha.2023.114546.

[89] B.M. Wolpin, A.F. Hezel, T. Abrams, L.S. Blaszkowsky, J.A. Meyerhardt, J. A. Chan, P.C. Enzinger, B. Allen, J.W. Clark, D.P. Ryan, C.S. Fuchs, Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer, J. Clin. Oncol. 27 (2009) 193–198, https://doi.org/10.1200/JCO.2008.18.9514.

[90] M.M. Javle, R.T. Shroff, H. Xiong, G.A. Varadhachary, D. Fogelman, S.A. Reddy, D. Davis, Y. Zhang, R.A. Wolff, J.L. Abbruzzese, Inhibition of the mammalian target of rapamycin (mTOR) in advanced pancreatic cancer: results of two phase II studies, BMC Cancer 10 (2010) 368, https://doi.org/10.1186/1471-2407-10-368.

[91] H.J. Zeh, N. Bahary, B.A. Boone, A.D. Singhi, J.L. Miller-Ocuin, D.P. Normolle, A. H. Zureikat, M.E. Hogg, D.L. Bartlett, K.K. Lee, A. Tsung, J.W. Marsh, P. Murthy, D. Tang, N. Seiser, R.K. Amaravadi, V. Espina, L. Liotta, M.T. Lotze, A randomized phase II preoperative study of autophagy inhibition with high-dose hydroxychloroquine and gemcitabine/nab-paclitaxel in pancreatic cancer patients, Clin. Cancer Res. 26 (2020) 3126–3134, https://doi.org/10.1158/1078-0432.CCR-19-4042.

[92] J. Li, N. Hou, A. Faried, S. Tsutsumi, H. Kuwano, Inhibition of autophagy augments 5-fluorouracil chemotherapy in human colon cancer in vitro and in vivo model, Eur. J. Cancer 46 (2010) 1900–1909, https://doi.org/10.1016/j.ejca.2010.02.021.

[93] L. Rong, Z. Li, X. Leng, H. Li, Y. Ma, Y. Chen, F. Song, Salidroside induces apoptosis and protective autophagy in human gastric cancer AGS cells through the PI3K/Akt/mTOR pathway, Biomed. Pharmacother. 122 (2020) 109726, https://doi.org/10.1016/j.biopha.2019.109726.

[94] C.-H. Chien, W.-B. Yang, J.-Y. Chuang, J.-S. Lee, W.-A. Liao, C.-Y. Huang, P.-Y. Chen, A.-C. Wu, S.-T. Yang, C.-C. Lai, P.-I. Chi, J.-M. Chu, S.M. Cheng, C.-C. Liu, D.-Y. Hwang, S.-H. Chen, K.-Y. Chang, SH3GLB1-related autophagy mediates mitochondrial metabolism to acquire resistance against temozolomide in glioblastoma, J. Exp. Clin. Cancer Res. 41 (2022) 220, https://doi.org/10.1186/s13046-022-02429-8.

[95] Y. Wang, H. Lei, B. Yan, S. Zhang, B. Xu, M. Lin, X. Shuai, J. Huang, J. Pang, Tumor acidity-activatable macromolecule autophagy inhibitor and immune checkpoint blockade for robust treatment of prostate cancer, Acta Biomater. 168 (2023) 593–605, https://doi.org/10.1016/j.actbio.2023.07.018.

[96] D. Eberli, B. Kranzbühler, A. Mortezavi, T. Sulser, S. Salemi, Apalutamide in combination with autophagy inhibitors improves treatment effects in prostate cancer cells, Urol. Oncol.: Seminars and Original Investigations 38 (2020) 683.e19–683.e26, https://doi.org/10.1016/j.urolonc.2020.04.030.

[97] Y. Miyazawa, Y. Sekine, D. Oka, S. Nakazawa, Y. Tsuji, H. Nakayama, K. Suzuki, Simvastatin induces autophagy and inhibits proliferation in prostate cancer cells, Anticancer Res. 43 (2023) 5377–5386, https://doi.org/10.21873/anticanres.16741.

[98] Z.J. Yang, C.E. Chee, S. Huang, F.A. Sinicrope, The role of autophagy in cancer: therapeutic implications, Mol. Cancer Therapeut. 10 (2011) 1533–1541, https://doi.org/10.1158/1535-7163.MCT-11-0047.

[99] J.Y. Guo, X. Teng, S.V. Laddha, S. Ma, S.C. Van Nostrand, Y. Yang, S. Khor, C. S. Chan, J.D. Rabinowitz, E. White, Autophagy provides metabolic substrates to maintain energy charge and nucleotide pools in Ras-driven lung cancer cells, Genes Dev. 30 (2016) 1704–1717, https://doi.org/10.1101/gad.283416.116.

[100] E.E. Mowers, M.N. Sharifi, K.F. Macleod, Functions of autophagy in the tumor microenvironment and cancer metastasis, FEBS J. 285 (2018) 1751–1766, https://doi.org/10.1111/febs.14388.

[101] X. Wang, Z. Li, Z. Gao, Q. Li, L. Jiang, C. Geng, X. Yao, X. Shi, Y. Liu, J. Cao, Cadmium induces cell growth in A549 and HELF cells via autophagy-dependent glycolysis, Toxicol. Vitro 66 (2020) 104834, https://doi.org/10.1016/j.tiv.2020.104834.

[102] J. Mei Hasenbilige, M.B. Dlamini, Z. Gao, L. Jiang, Q. Li, C. Geng, X. Shi, Y. Liu, Y. Kong, J. Cao, A requirement for autophagy in HMGA2-induced metabolic reprogramming to support Cd-induced migration, Toxicology 462 (2021) 152928, https://doi.org/10.1016/j.tox.2021.152928.
[103] C. Gerada, K.M. Ryan, Autophagy, the innate immune response and cancer, Mol. Oncol. 14 (2020) 1913–1929, https://doi.org/10.1002/1878-0261.12774.
[104] F. Ma, M.-G. Ding, Y.-Y. Lei, L.-H. Luo, S. Jiang, Y.-H. Feng, X.-L. Liu, SKIL facilitates tumorigenesis and immune escape of NSCLC via upregulating TAZ/autophagy axis, Cell Death Dis. 11 (2020) 1028, https://doi.org/10.1038/s41419-020-03200-7.
[105] X.H. Liang, S. Jackson, M. Seaman, K. Brown, B. Kempkes, H. Hibshoosh, B. Levine, Induction of autophagy and inhibition of tumorigenesis by beclin 1, Nature 402 (1999) 672–676, https://doi.org/10.1038/45257.
[106] V.M. Aita, X.H. Liang, V.V.V.S. Murty, D.L. Pincus, W. Yu, E. Cayanis, S. Kalachikov, T.C. Gilliam, B. Levine, Cloning and genomic organization of beclin 1, a candidate tumor suppressor gene on chromosome 17q21, Genomics 59 (1999) 59–65, https://doi.org/10.1006/geno.1999.5851.
[107] T. Marsh, C.M. Kenific, D. Suresh, H. Gonzalez, E.R. Shamir, W. Mei, A. Tankka, A.M. Leidal, S. Kalavacherla, K. Woo, Z. Werb, J. Debnath, Autophagic degradation of NBR1 restricts metastatic outgrowth during mammary tumor progression, Dev. Cell 52 (2020) 591–604.e6, https://doi.org/10.1016/j.devcel.2020.01.025.
[108] L. Poillet-Perez, G. Despouy, R. Delage-Mourroux, M. Boyer-Guittaut, Interplay between ROS and autophagy in cancer cells, from tumor initiation to cancer therapy, Redox Biol. 4 (2014) 184, https://doi.org/10.1016/j.redox.2014.12.003.
[109] A. Pandey, P. Kakani, S. Shukla, CTCF and BORIS-mediated autophagy regulation via alternative splicing of BNIP3L in breast cancer, J. Biol. Chem. 300 (2024), https://doi.org/10.1016/j.jbc.2024.107416.
[110] T. Rzymski, M. Milani, L. Pike, F. Buffa, H.R. Mellor, L. Winchester, I. Pires, E. Hammond, I. Ragoussis, A.L. Harris, Regulation of autophagy by ATF4 in response to severe hypoxia, Oncogene 29 (2010) 4424–4435, https://doi.org/10.1038/onc.2010.191.
[111] Y. Duan, X. Tian, Q. Liu, J. Jin, J. Shi, Y. Hou, Role of autophagy on cancer immune escape, Cell Commun. Signal. 19 (2021) 91, https://doi.org/10.1186/s12964-021-00769-0.
[112] C.-H. Choi, Y.-K. Jung, S.-H. Oh, Autophagy induction by capsaicin in malignant human breast cells is modulated by p38 and extracellular signal-regulated mitogen-activated protein kinases and retards cell death by suppressing endoplasmic reticulum stress-mediated apoptosis, Mol. Pharmacol. 78 (2010) 114–125, https://doi.org/10.1124/mol.110.063495.
[113] J. Gillson, Y.S.A. El-Aziz, L.Y.W. Leck, P.J. Jansson, N. Pavlakis, J.S. Samra, A. Mittal, S. Sahni, Autophagy: a key player in pancreatic cancer progression and a potential drug target, Cancers 14 (2022) 3528, https://doi.org/10.3390/cancers14143528.
[114] S. Yang, X. Wang, G. Contino, M. Liesa, E. Sahin, H. Ying, A. Bause, Y. Li, J. M. Stommel, G. Dell'Antonio, J. Mautner, G. Tonon, M. Haigis, O.S. Shirihai, C. Doglioni, N. Bardeesy, A.C. Kimmelman, Pancreatic cancers require autophagy for tumor growth, Genes Dev. 25 (2011) 717–729, https://doi.org/10.1101/gad.2016111.
[115] B. Marchand, M.-A. Poulin, C. Lawson, L.-H. Tai, S. Jean, M.-J. Boucher, Gemcitabine promotes autophagy and lysosomal function through ERK- and TFEB-dependent mechanisms, Cell Death Dis. 9 (2023) 45, https://doi.org/10.1038/s41420-023-01342-z.
[116] E. Hessmann, S.A. Johnsen, J.T. Siveke, V. Ellenrieder, Epigenetic treatment of pancreatic cancer: is there a therapeutic perspective on the horizon? Gut 66 (2017) 168–179, https://doi.org/10.1136/gutjnl-2016-312539.
[117] K. Görgülü, K.N. Diakopoulos, J. Ai, B. Schoeps, D. Kabacaoglu, A.-F. Karpathaki, K.J. Ciecielski, E. Kaya-Aksoy, D.A. Ruess, A. Berninger, M. Kowalska, M. Stevanovic, S.M. Wörmann, T. Wartmann, Y. Zhao, W. Halangk, S. Voronina, A. Tepikin, A.M. Schlitter, K. Steiger, A. Artati, J. Adamski, M. Aichler, A. Walch, M. Jastroch, G. Hartleben, C.S. Mantzoros, W. Weichert, R.M. Schmid, S. Herzig, A. Krüger, B. Sainz, M. Lesina, H. Algül, Levels of the autophagy-related 5 protein affect progression and metastasis of pancreatic tumors in mice, Gastroenterology 156 (2019) 203–217.e20, https://doi.org/10.1053/j.gastro.2018.09.053.
[118] A. Yang, G. Herter-Sprie, H. Zhang, E.Y. Lin, D. Biancur, X. Wang, J. Deng, J. Hai, S. Yang, K.-K. Wong, A.C. Kimmelman, Autophagy sustains pancreatic cancer growth through both cell-autonomous and nonautonomous mechanisms, Cancer Discov. 8 (2018) 276–287, https://doi.org/10.1158/2159-8290.CD-17-0952.
[119] The 2021 WHO Classification of Tumors of the Central Nervous System: a Summary, (n.d.).
[120] J.R. Hill, N. Kuriyama, H. Kuriyama, M.A. Israel, Molecular genetics of brain tumors, Arch. Neurol. 56 (1999) 439, https://doi.org/10.1001/archneur.56.4.439.
[121] S. Tamrakar, M. Yashiro, T. Kawashima, T. Uda, Y. Terakawa, Y. Kuwae, M. Ohsawa, K. Ohata, Clinicopathological significance of autophagy-related proteins and its association with genetic alterations in gliomas, Anticancer Res. 39 (2019) 1233–1242, https://doi.org/10.21873/anticanres.13233.
[122] N. Gammoh, J. Fraser, C. Puente, H.M. Syred, H. Kang, T. Ozawa, D. Lam, J. C. Acosta, A.J. Finch, E. Holland, X. Jiang, Suppression of autophagy impedes glioblastoma development and induces senescence, Autophagy 12 (2016) 1431–1439, https://doi.org/10.1080/15548627.2016.1190053.
[123] G. Bellot, R. Garcia-Medina, P. Gounon, J. Chiche, D. Roux, J. Pouysségur, N. M. Mazure, Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains, Mol. Cell Biol. 29 (2009) 2570–2581, https://doi.org/10.1128/MCB.00166-09.
[124] M. Zou, W. Zhu, L. Wang, L. Shi, R. Gao, Y. Ou, X. Chen, Z. Wang, A. Jiang, K. Liu, M. Xiao, P. Ni, D. Wu, W. He, G. Sun, P. Li, S. Zhai, X. Wang, G. Hu, AEG-1/MTDH-activated autophagy enhances human malignant glioma susceptibility to TGF-β1-triggered epithelial-mesenchymal transition, Oncotarget 7 (2016) 13122–13138, https://doi.org/10.18632/oncotarget.7536.
[125] M. Zhao, Y. Zhang, Y. Jiang, K. Wang, X. Wang, D. Zhou, Y. Wang, R. Yu, X. Zhou, YAP promotes autophagy and progression of gliomas via upregulating HMGB1, J. Exp. Clin. Cancer Res. 40 (2021) 99, https://doi.org/10.1186/s13046-021-01897-8.
[126] S. Liu, X. Zhang, W. Wang, X. Li, X. Sun, Y. Zhao, Q. Wang, Y. Li, F. Hu, H. Ren, Metabolic reprogramming and therapeutic resistance in primary and metastatic breast cancer, Mol. Cancer 23 (2024) 261, https://doi.org/10.1186/s12943-024-02165-x.
[127] J. Zhao, X. Ma, P. Gao, X. Han, P. Zhao, F. Xie, M. Liu, Advancing glioblastoma treatment by targeting metabolism, Neoplasia 51 (2024) 100985, https://doi.org/10.1016/j.neo.2024.100985.
[128] J. Lu, L. He, C. Behrends, M. Araki, K. Araki, Q. Jun Wang, J.M. Catanzaro, S. L. Friedman, W.-X. Zong, M.I. Fiel, M. Li, Z. Yue, NRBF2 regulates autophagy and prevents liver injury by modulating Atg14L-linked phosphatidylinositol-3 kinase III activity, Nat. Commun. 5 (2014) 3920, https://doi.org/10.1038/ncomms4920.
[129] J. Kim, H. Kang, B. Son, M.-J. Kim, J. Kang, K.H. Park, J. Jeon, S. Jo, H.Y. Kim, H. Youn, B. Youn, NRBF2-mediated autophagy contributes to metabolite replenishment and radioresistance in glioblastoma, Exp. Mol. Med. 54 (2022) 1872–1885, https://doi.org/10.1038/s12276-022-00873-2.
[130] D.J. Kloosterman, L. Akkari, Macrophages at the interface of the co-evolving cancer ecosystem, Cell 186 (2023) 1627–1651, https://doi.org/10.1016/j.cell.2023.02.020.
[131] F. Khan, L. Pang, M. Dunterman, M.S. Lesniak, A.B. Heimberger, P. Chen, Macrophages and microglia in glioblastoma: heterogeneity, plasticity, and therapy, J. Clin. Investig. 133 (2023) e163446, https://doi.org/10.1172/JCI163446.
[132] Y. Fan, Y. Wang, J. Zhang, X. Dong, P. Gao, K. Liu, C. Ma, G. Zhao, Breaking bad: autophagy tweaks the interplay between glioma and the tumor immune microenvironment, Front. Immunol. 12 (2021) 746621, https://doi.org/10.3389/fimmu.2021.746621.
[133] Z. Jin, X. Sun, Y. Wang, C. Zhou, H. Yang, S. Zhou, Regulation of autophagy fires up the cold tumor microenvironment to improve cancer immunotherapy, Front. Immunol. 13 (2022) 1018903, https://doi.org/10.3389/fimmu.2022.1018903.
[134] Q. Xia, M. Xu, P. Zhang, L. Liu, X. Meng, L. Dong, Therapeutic potential of autophagy in glioblastoma treatment with phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin signaling pathway inhibitors, Front. Oncol. 10 (2020) 572904, https://doi.org/10.3389/fonc.2020.572904.
[135] J. Long, Q. He, Y. Yin, X. Lei, Z. Li, W. Zhu, The effect of miRNA and autophagy on colorectal cancer, Cell Prolif. 53 (2020) e12900, https://doi.org/10.1111/cpr.12900.
[136] R.M. Mohammad, I. Muqbil, L. Lowe, C. Yedjou, H.-Y. Hsu, L.-T. Lin, M. D. Siegelin, C. Fimognari, N.B. Kumar, Q.P. Dou, H. Yang, A.K. Samadi, G. L. Russo, C. Spagnuolo, S.K. Ray, M. Chakrabarti, J.D. Morre, H.M. Coley, K. Honoki, H. Fujii, A.G. Georgakilas, A. Amedei, E. Niccolai, A. Amin, S. S. Ashraf, W.G. Helferich, X. Yang, C.S. Boosani, G. Guha, D. Bhakta, M.R. Ciriolo, K. Aquilano, S. Chen, S.I. Mohammed, W.N. Keith, A. Bilsland, D. Halicka, S. Nowsheen, A.S. Azmi, Broad targeting of resistance to apoptosis in cancer, Semin. Cancer Biol. 35 (2015) S78–S103, https://doi.org/10.1016/j.semcancer.2015.03.001.
[137] S. Wu, X. Wang, J. Chen, Y. Chen, Autophagy of cancer stem cells is involved with chemoresistance of colon cancer cells, Biochem. Biophys. Res. Commun. 434 (2013) 898–903, https://doi.org/10.1016/j.bbrc.2013.04.053.
[138] H.-Z. Yang, Y. Ma, Y. Zhou, L.-M. Xu, X.-J. Chen, W.-B. Ding, H.-B. Zou, Autophagy contributes to the enrichment and survival of colorectal cancer stem cells under oxaliplatin treatment, Cancer Lett. 361 (2015) 128–136, https://doi.org/10.1016/j.canlet.2015.02.045.
[139] D.B. Longley, D.P. Harkin, P.G. Johnston, 5-fluorouracil: mechanisms of action and clinical strategies, Nat. Rev. Cancer 3 (2003) 330–338, https://doi.org/10.1038/nrc1074.
[140] W. Li, C. Zhou, L. Yu, Z. Hou, H. Liu, L. Kong, Y. Xu, J. He, J. Lan, Q. Ou, Y. Fang, Z. Lu, X. Wu, Z. Pan, J. Peng, J. Lin, Tumor-derived lactate promotes resistance to bevacizumab treatment by facilitating autophagy enhancer protein RUBCNL expression through histone H3 lysine 18 lactylation (H3K18la) in colorectal cancer, Autophagy 20 (2024) 114–130, https://doi.org/10.1080/15548627.2023.2249762.
[141] M.-Y. Zhang, W.-F. Gou, S. Zhao, X.-Y. Mao, Z.-H. Zheng, Y. Takano, H.-C. Zheng, Beclin 1 expression is closely linked to colorectal carcinogenesis and distant metastasis of colorectal carcinoma, Int. J. Mol. Sci. 15 (2014) 14372–14385, https://doi.org/10.3390/ijms150814372.
[142] C.H. Ahn, E.G. Jeong, J.W. Lee, M.S. Kim, S.H. Kim, S.S. Kim, N.J. Yoo, S.H. Lee, Expression of beclin-1, an autophagy-related protein, in gastric and colorectal cancers, APMIS 115 (2007) 1344–1349, https://doi.org/10.1111/j.1600-0463.2007.00858.x.
[143] K. Koneri, T. Goi, Y. Hirono, K. Katayama, A. Yamaguchi, Beclin 1 gene inhibits tumor growth in colon cancer cell lines, Anticancer Res. 27 (2007) 1453–1457.
[144] L. Taraborrelli, Y. Şenbabaoğlu, L. Wang, J. Lim, K. Blake, N. Kljavin, S. Gierke, A. Scherl, J. Ziai, E. McNamara, M. Owyong, S. Rao, A.K. Calviello, D. Oreper, S. Jhunjhunwala, G. Argiles, J. Bendell, T.W. Kim, F. Ciardiello, M. J. Wongchenko, F.J. de Sauvage, F. de Sousa E Melo, Y. Yan, N.R. West, A. Murthy, Tumor-intrinsic expression of the autophagy gene Atg16l1 suppresses

anti-tumor immunity in colorectal cancer, Nat. Commun. 14 (2023) 5945, https://doi.org/10.1038/s41467-023-41618-7.
[145] E. Ziparo, S. Petrungaro, E. Marini, D. Starace, S. Conti, A. Facchiano, A. Filippini, C. Giampietri, Autophagy in prostate cancer and androgen suppression therapy, Indian J. Manag. Sci. 14 (2013) 12090–12106, https://doi.org/10.3390/ijms140612090.
[146] M. Ashrafizadeh, M.D.A. Paskeh, S. Mirzaei, M.H. Gholami, A. Zarrabi, F. Hashemi, K. Hushmandi, M. Hashemi, N. Nabavi, F. Crea, J. Ren, D.J. Klionsky, A.P. Kumar, Y. Wang, Targeting autophagy in prostate cancer: preclinical and clinical evidence for therapeutic response, J. Exp. Clin. Cancer Res. 41 (2022) 105, https://doi.org/10.1186/s13046-022-02293-6.
[147] Y. Huang, X. Jiang, X. Liang, G. Jiang, Molecular and cellular mechanisms of castration resistant prostate cancer, Oncol. Lett. 15 (2018) 6063–6076, https://doi.org/10.3892/ol.2018.8123.
[148] I. Coutinho, T.K. Day, W.D. Tilley, L.A. Selth, Androgen receptor signaling in castration-resistant prostate cancer: a lesson in persistence, Endocr. Relat. Cancer 23 (2016) T179–T197, https://doi.org/10.1530/ERC-16-0422.
[149] J. Sha, Q. Han, C. Chi, Y. Zhu, J. Pan, B. Dong, Y. Huang, W. Xia, W. Xue, Upregulated KDM4B promotes prostate cancer cell proliferation by activating autophagy, J. Cell. Physiol. 235 (2020) 2129–2138, https://doi.org/10.1002/jcp.29117.
[150] M. Ding, C.-Y. Jiang, Y. Zhang, J. Zhao, B.-M. Han, S.-J. Xia, SIRT7 depletion inhibits cell proliferation and androgen-induced autophagy by suppressing the AR signaling in prostate cancer, J. Exp. Clin. Cancer Res. 39 (2020) 28, https://doi.org/10.1186/s13046-019-1516-1.
[151] J. Lu, C. Zhong, J. Luo, F. Shu, D. Lv, Z. Liu, X. Tan, S. Wang, K. Wu, T. Yang, W. Zhong, B. Wang, Y. Chen, Y. Li, Z. Jia, Y. Zou, W. Zhong, X. Mao, HnRNP-L-regulated circCSPP1/miR-520h/EGR1 axis modulates autophagy and promotes progression in prostate cancer, Mol. Ther. Nucleic Acids 26 (2021) 927–944, https://doi.org/10.1016/j.omtn.2021.10.006.
[152] S. Niture, L. Tricoli, Q. Qi, S. Gadi, K. Hayes, D. Kumar, MicroRNA-99b-5p targets mTOR/AR axis, induces autophagy and inhibits prostate cancer cell proliferation, Tumour Biol 44 (2022) 107–127, https://doi.org/10.3233/TUB-211568.
[153] D. Loizzo, S.D. Pandolfo, D. Rogers, C. Cerrato, N.A. Di Meo, R. Autorino, V. Mirone, M. Ferro, C. Porta, A. Stella, C. Bizzoca, L. Vincenti, M. Spilotros, M. Rutigliano, M. Battaglia, P. Ditonno, G. Lucarelli, Novel insights into autophagy and prostate cancer: a comprehensive review, Indian J. Manag. Sci. 23 (2022) 3826, https://doi.org/10.3390/ijms23073826.
[154] M. Kocak, S. Ezazi Erdi, G. Jorba, I. Maestro, J. Farrés, V. Kirkin, A. Martinez, O. Pless, Targeting autophagy in disease: established and new strategies, Autophagy 18 (2022) 473–495, https://doi.org/10.1080/15548627.2021.1936359.
[155] H. Dai, W. Hu, L. Zhang, F. Jiang, X. Mao, G. Yang, L. Li, FGF21 facilitates autophagy in prostate cancer cells by inhibiting the PI3K–Akt–mTOR signaling pathway, Cell Death Dis. 12 (2021) 303, https://doi.org/10.1038/s41419-021-03588-w.
[156] Y. Qiao, J.E. Choi, J.C. Tien, S.A. Simko, T. Rajendiran, J.N. Vo, A.D. Delekta, L. Wang, L. Xiao, N.B. Hodge, P. Desai, S. Mendoza, K. Juckette, A. Xu, T. Soni, F. Su, R. Wang, X. Cao, J. Yu, I. Kryczek, X.-M. Wang, X. Wang, J. Siddiqui, Z. Wang, A. Bernard, E. Fernandez-Salas, N.M. Navone, S.J. Ellison, K. Ding, E.-L. Eskelinen, E.I. Heath, D.J. Klionsky, W. Zou, A.M. Chinnaiyan, Autophagy inhibition by targeting PIKfyve potentiates response to immune checkpoint blockade in prostate cancer, Nat. Can. (Ott.) 2 (2021) 978–993, https://doi.org/10.1038/s43018-021-00237-1.
[157] D.C. Wallace, A mitochondrial paradigm of metabolic and degenerative diseases, Aging, and Cancer: A Dawn for Evolutionary Medicine (2005).
[158] M.A. Rahman, M.N. Park, M.H. Rahman, M.M. Rashid, R. Islam, M.J. Uddin, M. A. Hannan, B. Kim, p53 modulation of autophagy signaling in cancer therapies: perspectives mechanism and therapeutic targets, Front. Cell Dev. Biol. 10 (2022) 761080, https://doi.org/10.3389/fcell.2022.761080.
[159] M.N. Nakrani, R.H. Wineland, F. Anjum, Physiology, glucose metabolism, in: StatPearls, StatPearls Publishing, Treasure Island (FL), 2024. http://www.ncbi.nlm.nih.gov/books/NBK560599/.
[160] Y. Chu, Y. Chang, W. Lu, X. Sheng, S. Wang, H. Xu, J. Ma, Regulation of autophagy by glycolysis in cancer, Cancer Manag. Res. 12 (2020) 13259–13271, https://doi.org/10.2147/CMAR.S279672.
[161] M. Kitada, D. Koya, Autophagy in metabolic disease and ageing, Nat. Rev. Endocrinol. 17 (2021) 647–661, https://doi.org/10.1038/s41574-021-00551-9.
[162] M. Kawaguchi, S. Aoki, T. Hirao, M. Morita, K. Ito, Autophagy is an important metabolic pathway to determine leukemia cell survival following suppression of the glycolytic pathway, Biochem. Biophys. Res. Commun. 474 (2016) 188–192, https://doi.org/10.1016/j.bbrc.2016.04.098.
[163] L. Brohée, O. Peulen, B. Nusgens, V. Castronovo, M. Thiry, A.C. Colige, C. F. Deroanne, Propranolol sensitizes prostate cancer cells to glucose metabolism inhibition and prevents cancer progression, Sci. Rep. 8 (2018) 7050, https://doi.org/10.1038/s41598-018-25340-9.
[164] P.V. Dellorusso, M.A. Proven, F.J. Calero-Nieto, X. Wang, C.A. Mitchell, F. Hartmann, M. Amouzgar, P. Favaro, A. DeVilbiss, J.W. Swann, T.T. Ho, Z. Zhao, S.C. Bendall, S. Morrison, B. Göttgens, E. Passegué, Autophagy counters inflammation-driven glycolytic impairment in aging hematopoietic stem cells, Cell Stem Cell 31 (2024) 1020–1037.e9, https://doi.org/10.1016/j.stem.2024.04.020.
[165] Z. Feng, R.W. Hanson, N.A. Berger, A. Trubitsyn, Reprogramming of energy metabolism as a driver of aging, Oncotarget 7 (2016) 15410–15420, https://doi.org/10.18632/oncotarget.7645.
[166] C. Wu, S.A. Khan, A.J. Lange, Regulation of glycolysis—role of insulin, Exp. Gerontol. 40 (2005) 894–899, https://doi.org/10.1016/j.exger.2005.08.002.
[167] X. Ye, M. Li, T. Hou, T. Gao, W. Zhu, Y. Yang, Sirtuins in glucose and lipid metabolism, Oncotarget 8 (2016) 1845–1859, https://doi.org/10.18632/oncotarget.12157.
[168] Z. Luo, M. Tian, G. Yang, Q. Tan, Y. Chen, G. Li, Q. Zhang, Y. Li, P. Wan, J. Wu, Hypoxia signaling in human health and diseases: implications and prospects for therapeutics, Signal Transduct. Targeted Ther. 7 (2022) 1–30, https://doi.org/10.1038/s41392-022-01080-1.
[169] I. Daskalaki, I. Gkikas, N. Tavernarakis, Hypoxia and selective autophagy in cancer development and therapy, Front. Cell Dev. Biol. 6 (2018), https://doi.org/10.3389/fcell.2018.00104.
[170] D.R. Ryu, M.R. Yu, K.H. Kong, H. Kim, S.H. Kwon, J.S. Jeon, D.C. Han, H. Noh, Sirt1-hypoxia-inducible factor-1α interaction is a key mediator of tubulointerstitial damage in the aged kidney, Aging Cell 18 (2019) e12904, https://doi.org/10.1111/acel.12904.
[171] H.-Y. Joo, M. Yun, J. Jeong, E.-R. Park, H.-J. Shin, S.R. Woo, J.K. Jung, Y.-M. Kim, J.-J. Park, J. Kim, K.-H. Lee, SIRT1 deacetylates and stabilizes hypoxia-inducible factor-1α (HIF-1α) *via* direct interactions during hypoxia, Biochem. Biophys. Res. Commun. 462 (2015) 294–300, https://doi.org/10.1016/j.bbrc.2015.04.119.
[172] X.-W. Lin, L. Tang, J. Yang, W.-H. Xu, HIF-1 regulates insect lifespan extension by inhibiting c-Myc-TFAM signaling and mitochondrial biogenesis, Biochim. Biophys. Acta 1863 (2016) 2594–2603, https://doi.org/10.1016/j.bbamcr.2016.07.007.
[173] S. Xiong, G. Salazar, N. Patrushev, R.W. Alexander, FoxO1 mediates an autofeedback loop regulating SIRT1 expression, J. Biol. Chem. 286 (2011) 5289–5299, https://doi.org/10.1074/jbc.M110.163667.
[174] M. Fulco, V. Sartorelli, Comparing and contrasting the roles of AMPK and SIRT1 in metabolic tissues, Cell Cycle 7 (2008) 3669–3679, https://doi.org/10.4161/cc.7.23.7164.
[175] J.K.L. Mak, C.E. McMurran, R.K. Halkola, P. Hall, K. Czene, J. Jylhävä, S. Hägg, Clinical biomarker-based biological aging and risk of cancer in the UK Biobank, Br. J. Cancer 129 (2023) 94–103, https://doi.org/10.1038/s41416-023-02288-w.
[176] A.A. Johnson, K. Akman, S.R.G. Calimport, D. Wuttke, A. Stolzing, J.P. de Magalhães, The role of DNA methylation in aging, rejuvenation, and age-related disease, Rejuvenation Res. 15 (2012) 483–494, https://doi.org/10.1089/rej.2012.1324.
[177] S. Gelino, M. Hansen, Autophagy - an emerging anti-aging mechanism, J. Clin. Exp. Pathol. Suppl 4 (2012), https://doi.org/10.4172/2161-0681.s4-006, 6.
[178] Y. Aman, T.S.- Medina, M. Hansen, R.I. Morimoto, A.K. Simon, I. Bjedov, K. Palikaras, A. Simonsen, T. Johansen, N. Tavernarakis, D.C. Rubinsztein, L. Partridge, G. Kroemer, J. Labbadia, E.F. Fang, Autophagy in healthy aging and disease, Nat. Aging 1 (2021) 634–650, https://doi.org/10.1038/s43587-021-00098-4.
[179] Á.F. Fernández, S. Sebti, Y. Wei, Z. Zou, M. Shi, K.L. McMillan, C. He, T. Ting, Y. Liu, W.-C. Chiang, D.K. Marciano, G.G. Schiattarella, G. Bhagat, O.W. Moe, M. C. Hu, B. Levine, Disruption of the beclin 1-BCL2 autophagy regulatory complex promotes longevity in mice, Nature 558 (2018) 136–140, https://doi.org/10.1038/s41586-018-0162-7.
[180] G. Juhász, B. Erdi, M. Sass, T.P. Neufeld, Atg7-dependent autophagy promotes neuronal health, stress tolerance, and longevity but is dispensable for metamorphosis in Drosophila, Genes Dev. 21 (2007) 3061–3066, https://doi.org/10.1101/gad.1600707.
[181] E. Morselli, M.C. Maiuri, M. Markaki, E. Megalou, A. Pasparaki, K. Palikaras, A. Criollo, L. Galluzzi, S.A. Malik, I. Vitale, M. Michaud, F. Madeo, N. Tavernarakis, G. Kroemer, Caloric restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy, Cell Death Dis. 1 (2010) e10, https://doi.org/10.1038/cddis.2009.8.
[182] J.R. Rohde, M.E. Cardenas, Nutrient signaling through TOR kinases controls gene expression and cellular differentiation in fungi, in: G. Thomas, D.M. Sabatini, M. N. Hall (Eds.), TOR: Target of Rapamycin, Springer, Berlin, Heidelberg, 2004, pp. 53–72, https://doi.org/10.1007/978-3-642-18930-2_4.
[183] T. Beck, M.N. Hall, The TOR signalling pathway controls nuclear localization of nutrient-regulated transcription factors, Nature 402 (1999) 689–692, https://doi.org/10.1038/45287.
[184] J. Füllgrabe, M.A. Lynch-Day, N. Heldring, W. Li, R.B. Struijk, Q. Ma, O. Hermanson, M.G. Rosenfeld, D.J. Klionsky, B. Joseph, The histone H4 lysine 16 acetyltransferase hMOF regulates the outcome of autophagy, Nature 500 (2013) 468–471, https://doi.org/10.1038/nature12313.
[185] H.-W. Tang, J.-H. Weng, W.X. Lee, Y. Hu, L. Gu, S. Cho, G. Lee, R. Binari, C. Li, M. E. Cheng, A.-R. Kim, J. Xu, Z. Shen, C. Xu, J.M. Asara, J. Blenis, N. Perrimon, mTORC1-chaperonin CCT signaling regulates m6A RNA methylation to suppress autophagy, Proc. Natl. Acad. Sci. USA 118 (2021) e2021945118, https://doi.org/10.1073/pnas.2021945118.
[186] E.L. Greer, T.J. Maures, D. Ucar, A.G. Hauswirth, E. Mancini, J.P. Lim, B. A. Benayoun, Y. Shi, A. Brunet, Transgenerational epigenetic inheritance of longevity in Caenorhabditis elegans, Nature 479 (2011) 365–371, https://doi.org/10.1038/nature10572.
[187] Z. Ma, H. Wang, Y. Cai, H. Wang, K. Niu, X. Wu, H. Ma, Y. Yang, W. Tong, F. Liu, Z. Liu, Y. Zhang, R. Liu, Z.-J. Zhu, N. Liu, Epigenetic drift of H3K27me3 in aging links glycolysis to healthy longevity in Drosophila, Elife 7 (2018) e35368, https://doi.org/10.7554/eLife.35368.
[188] P.G. Rodríguez, J. Füllgrabe, B. Joseph, The hunger strikes back: an epigenetic memory for autophagy, Cell Death Differ. 30 (2023) 1404–1415, https://doi.org/10.1038/s41418-023-01159-4.

[189] F.-Z. Wei, Z. Cao, X. Wang, H. Wang, M.-Y. Cai, T. Li, N. Hattori, D. Wang, Y. Du, B. Song, L.-L. Cao, C. Shen, L. Wang, H. Wang, Y. Yang, D. Xie, F. Wang, T. Ushijima, Y. Zhao, W.-G. Zhu, Epigenetic regulation of autophagy by the methyltransferase EZH2 through an MTOR-dependent pathway, Autophagy 11 (2015) 2309–2322, https://doi.org/10.1080/15548627.2015.1117734.

[190] A.P. Siebold, R. Banerjee, F. Tie, D.L. Kiss, J. Moskowitz, P.J. Harte, Polycomb Repressive Complex 2 and Trithorax modulate Drosophila longevity and stress resistance, Proc. Natl. Acad. Sci. USA 107 (2010) 169–174, https://doi.org/10.1073/pnas.0907739107.

[191] T.J. Maures, E.L. Greer, A.G. Hauswirth, A. Brunet, The H3K27 demethylase UTX-1 regulates C. elegans lifespan in a germline-independent, insulin-dependent manner, Aging Cell 10 (2011) 980–990, https://doi.org/10.1111/j.1474-9726.2011.00738.x.

[192] P. González-Rodríguez, M. Cheray, L. Keane, P. Engskog-Vlachos, B. Joseph, ULK3-dependent activation of GLI1 promotes DNMT3A expression upon autophagy induction, Autophagy 18 (2022) 2769–2780, https://doi.org/10.1080/15548627.2022.2039993.

[193] P. González-Rodríguez, M. Cheray, J. Füllgrabe, M. Salli, P. Engskog-Vlachos, L. Keane, V. Cunha, A. Lupa, W. Li, Q. Ma, K. Dreij, M.G. Rosenfeld, B. Joseph, The DNA methyltransferase DNMT3A contributes to autophagy long-term memory, Autophagy 17 (2021) 1259–1277, https://doi.org/10.1080/15548627.2020.1816664.

[194] L. Varisli, O. Cen, S. Vlahopoulos, Dissecting pharmacological effects of chloroquine in cancer treatment: interference with inflammatory signaling pathways, Immunology 159 (2020) 257–278, https://doi.org/10.1111/imm.13160.

[195] R. Xu, Z. Ji, C. Xu, J. Zhu, The clinical value of using chloroquine or hydroxychloroquine as autophagy inhibitors in the treatment of cancers, Medicine (Baltim.) 97 (2018) e12912, https://doi.org/10.1097/MD.0000000000012912.

[196] T.R. Doeppner, C. Coman, D. Burdusel, D.-L. Ancuta, U. Brockmeier, D.N. Pirici, K. Yaoyun, D.M. Hermann, A. Popa-Wagner, Long-term treatment with chloroquine increases lifespan in middle-aged male mice possibly via autophagy modulation, proteasome inhibition and glycogen metabolism, Aging (Albany NY) 14 (2022) 4195, https://doi.org/10.18632/aging.204069.

[197] M. Qian, Z. Liu, L. Peng, X. Tang, F. Meng, Y. Ao, M. Zhou, M. Wang, X. Cao, B. Qin, Z. Wang, Z. Zhou, G. Wang, Z. Gao, J. Xu, B. Liu, Boosting ATM activity alleviates aging and extends lifespan in a mouse model of progeria, Elife 7 (2018) e34836, https://doi.org/10.7554/eLife.34836.

[198] K.L. Cook, A. Wärri, D.R. Soto-Pantoja, P.A. Clarke, M.I. Cruz, A. Zwart, R. Clarke, Hydroxychloroquine inhibits autophagy to potentiate antiestrogen responsiveness in ER+ breast cancer, Clin. Cancer Res. 20 (2014) 3222–3232, https://doi.org/10.1158/1078-0432.CCR-13-3227.

[199] N.P. Ozates, F. Soğutlu, F. Lerminoglu, B. Demir, C. Gunduz, B. Shademan, C. B. Avci, Effects of rapamycin and AZD3463 combination on apoptosis, autophagy, and cell cycle for resistance control in breast cancer, Life Sci. 264 (2021) 118643, https://doi.org/10.1016/j.lfs.2020.118643.

[200] N. Masaki, Y. Aoki, K. Obara, Y. Kubota, M. Bouvet, J. Miyazaki, R.M. Hoffman, Targeting autophagy with the synergistic combination of chloroquine and rapamycin as a novel effective treatment for well-differentiated liposarcoma, Cancer Genomics Proteomics 20 (2023) 317, https://doi.org/10.21873/cgp.20384.

[201] V. Martínez-Cisuelo, J. Gómez, I. García-Junceda, A. Naudí, R. Cabré, N. Mota-Martorell, M. López-Torres, M. González-Sánchez, R. Pamplona, G. Barja, Rapamycin reverses age-related increases in mitochondrial ROS production at complex I, oxidative stress, accumulation of mtDNA fragments inside nuclear DNA, and lipofuscin level, and increases autophagy, in the liver of middle-aged mice, Exp. Gerontol. 83 (2016) 130–138, https://doi.org/10.1016/j.exger.2016.08.002.

[202] J. Li, Y. Fan, Y. Zhang, Y. Liu, Y. Yu, M. Ma, Resveratrol induces autophagy and apoptosis in non-small-cell lung cancer cells by activating the NGFR-AMPK-mTOR pathway, Nutrients 14 (2022) 2413, https://doi.org/10.3390/nu14122413.

[203] M. Sugiyama, R. Kawahara-Miki, H. Kawana, K. Shirasuna, T. Kuwayama, H. Iwata, Resveratrol-induced mitochondrial synthesis and autophagy in oocytes derived from early antral follicles of aged cows, J. Reprod. Dev. 61 (2015) 251, https://doi.org/10.1262/jrd.2015-001.

[204] J. Kasznicki, A. Sliwinska, J. Drzewoski, Metformin in cancer prevention and therapy, Ann. Transl. Med. 2 (2014) 57, https://doi.org/10.3978/j.issn.2305-5839.2014.06.01.

[205] G. Blandino, M. Valerio, M. Cioce, F. Mori, L. Casadei, C. Pulito, A. Sacconi, F. Biagioni, G. Cortese, S. Galanti, C. Manetti, G. Citro, P. Muti, S. Strano, Metformin elicits anticancer effects through the sequential modulation of DICER and c-MYC, Nat. Commun. 3 (2012) 865, https://doi.org/10.1038/ncomms1859.

[206] B. Onken, M. Driscoll, Metformin induces a dietary restriction-like state and the oxidative stress response to extend C. elegans Healthspan via AMPK, LKB1, and SKN-1, PLoS One 5 (2010) e8758, https://doi.org/10.1371/journal.pone.0008758.

[207] I. Mohammed, M.D. Hollenberg, H. Ding, C.R. Triggle, A critical review of the evidence that metformin is a putative anti-aging drug that enhances healthspan and extends lifespan, Front. Endocrinol. 12 (2021), https://doi.org/10.3389/fendo.2021.718942.

[208] P. Senesi, A. Montesano, L. Luzi, R. Codella, S. Benedini, I. Terruzzi, Metformin treatment prevents sedentariness related damages in mice, J. Diabetes Res. 2016 (2016) 8274689, https://doi.org/10.1155/2016/8274689.

[209] Y.C. Wu, W.K.K. Wu, Y. Li, L. Yu, Z.J. Li, C.C.M. Wong, H.T. Li, J.J.Y. Sung, C. H. Cho, Inhibition of macroautophagy by bafilomycin A1 lowers proliferation and induces apoptosis in colon cancer cells, Biochem. Biophys. Res. Commun. 382 (2009) 451–456, https://doi.org/10.1016/j.bbrc.2009.03.051.

[210] Y. Yan, K. Jiang, P. Liu, X. Zhang, X. Dong, J. Gao, Q. Liu, M.P. Barr, Q. Zhang, X. Hou, S. Meng, P. Gong, Bafilomycin A1 induces caspase-independent cell death in hepatocellular carcinoma cells via targeting of autophagy and MAPK pathways, Sci. Rep. 6 (2016) 37052, https://doi.org/10.1038/srep37052.

[211] Z. Xie, Y. Xie, Y. Xu, H. Zhou, W. Xu, Q. Dong, Bafilomycin A1 inhibits autophagy and induces apoptosis in MG63 osteosarcoma cells, Mol. Med. Rep. 10 (2014) 1103–1107, https://doi.org/10.3892/mmr.2014.2281.

[212] J. Chicote, V.J. Yuste, J. Boix, J. Ribas, Cell death triggered by the autophagy inhibitory drug 3-methyladenine in growing conditions proceeds with DNA damage, Front. Pharmacol. 11 (2020), https://doi.org/10.3389/fphar.2020.580343.

[213] A. Ibrahim-Hashim, V. Estrella, Acidosis and cancer: from mechanism to neutralization, Cancer Metastasis Rev. 38 (2019) 149–155, https://doi.org/10.1007/s10555-019-09787-4.

[214] L.E. Low, C.K. Kong, W.-H. Yap, S.P. Siva, S.H. Gan, W.S. Siew, L.C. Ming, A. S. Lai-Foenander, S.K. Chang, W.-L. Lee, Y. Wu, K.-Y. Khaw, Y.S. Ong, B.T. Tey, S. K. Singh, K. Dua, D.K. Chellappan, B.-H. Goh, Hydroxychloroquine: key therapeutic advances and emerging nanotechnological landscape for cancer mitigation, Chem. Biol. Interact. 386 (2023) 110750, https://doi.org/10.1016/j.cbi.2023.110750.

[215] J. Li, S.G. Kim, J. Blenis, Rapamycin: one drug, many effects, Cell Metab. 19 (2014) 373–379, https://doi.org/10.1016/j.cmet.2014.01.001.

[216] M. Koushki, N. Amiri-Dashatan, N. Ahmadi, H. Abbaszadeh, M. Rezaei-Tavirani, Resveratrol: a miraculous natural compound for diseases treatment, Food Sci. Nutr. 6 (2018) 2473–2490, https://doi.org/10.1002/fsn3.855.

[217] A. Decensi, M. Puntoni, P. Goodwin, M. Cazzaniga, A. Gennari, B. Bonanni, S. Gandini, Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis, Cancer Prev. Res. 3 (2010) 1451–1461, https://doi.org/10.1158/1940-6207.CAPR-10-0157.

[218] M. De Santi, G. Baldelli, A. Diotallevi, L. Galluzzi, G.F. Schiavano, G. Brandi, Metformin prevents cell tumorigenesis through autophagy-related cell death, Sci. Rep. 9 (2019) 66, https://doi.org/10.1038/s41598-018-37247-6.

[219] V.N. Anisimov, L.M. Berstein, P.A. Egormin, T.S. Piskunova, I.G. Popovich, M. A. Zabezhinski, I.G. Kovalenko, T.E. Poroshina, A.V. Semenchenko, M. Provinciali, F. Re, C. Franceschi, Effect of metformin on life span and on the development of spontaneous mammary tumors in HER-2/neu transgenic mice, Exp. Gerontol. 40 (2005) 685–693, https://doi.org/10.1016/j.exger.2005.07.007.