**Abstract:** Autophagy and the lysosomal system, together referred to as the autophagolysosomal system, is a cellular quality control network which maintains cellular health and homeostasis by removing cellular waste including protein aggregates, damaged organelles, and invading pathogens. As such, the autophagolysosomal system has roles in a variety of pathophysiological disorders, including cancer, neurological disorders, immune- and inflammation-related diseases, and metabolic alterations, among others. The autophagolysosomal system is controlled by TFEB, a master transcriptional regulator driving the expression of multiple genes, including autophagolysosomal components. Importantly, Reactive Oxygen Species (ROS) production and control are key aspects of the physiopathological roles of the autophagolysosomal system, and may hold a key for synergistic therapeutic interventions. In this study, we reviewed our current knowledge on the biology and physiopathology of the autophagolysosomal system, and its potential for therapeutic intervention in cancer.

**Keywords:** TFEB; autophagy; mTOR; AMPK; lysosomes; cancer; nanoparticles

### 1. Introduction

The regulation of autophagy and the dynamics of the lysosomal system are intertwined to ensure cellular health and quality [1–3], and their disruption contributes to the physiopathology of several diseases, including cancer, neurodegeneration, metabolic and ageing-related disorders, and inflammatory diseases [1,4,5]. Transcription factor EB (TFEB), one of the four members of the MiTF/TFE3 family [6], is a master transcriptional regulator of both autophagy and lysosomal components [7–11]. In addition, TFEB transcriptionally regulates the expression of genes involved in mitochondrial quality control [12], lipid metabolism [13], and lysosomal exocytosis [14].

Cancer is one of the prime causes of death worldwide [15]. Despite recent advances, this disease still poses a major challenge to public health [15]. Several signaling pathways are frequently altered in cancer [16–18], among which autophagy regulatory networks and the lysosomal system represent prominent examples with potential therapeutic implications [19–24]. Lysosomotropic drugs such as chloroquine and hydroxychloroquine are currently being tested in the clinic [24–26]. Several other drugs, which inhibit lysosomal function, have shown efficacy against different types of cancers [20,24], not only inhibiting...
lysosomal function, but also disrupting autophagy-dependent processes, as lysosomal
damage affects terminal steps of autophagy [23,24]. Several drugs targeting autophagy
inhibit proliferation across several cancer-cell types [20,24].

TFEB and related proteins frequently behave as oncoproteins, as they have a key role
in the progression of different cancer types [27,28] through the transcriptional control of
different processes contributing to tumor-cell survival, metastasis, and chemoresistance [28].
TFEB does not only directly control autophagy and lysosomal dynamics, but also regulates
mechanistic Target of Rapamycin (mTOR) [29], a signaling kinase onto which nutrient
sensing and anabolic cues converge and which negatively regulates autophagy [30–33]. In
this study, we reviewed the contributions of autophagy and the lysosomal system to cancer
progression and chemoresistance, and the roles of TFEB therein.

2. Autophagy: An Essential Homeostatic Process

Autophagy is a homeostatic process that delivers cell components and structures to
lysosomes for degradation and recycling. Autophagy gets rid of cytosolic waste, including
damaged organelles and protein aggregates, and contributes to the clearance of invading
pathogens. The autophagic machinery is conserved from yeast to mammals [34], and its
components control distinct steps to achieve a tight control of this process. Autophagy is
initiated by the Unc-51-like autophagy-activating kinase (ULK1) complex, which receives
input on cell energy balance, nutrient availability, and growth signaling from mTOR
and AMP-activated protein kinase (AMPK) signaling networks [30,31,33,35] (Figure 1).
Apart from nutrient availability, viral infections can positively regulate the autophagic
process, both directly, through the influence of viral elements on autophagic proteins, and
indirectly, through the activation of cellular-stress responses, which, in turn, stimulate
autophagy [36,37].

Autophagy-related proteins 2 and 9 (ATG2 and ATG9) provide phospholipids for
the nucleation of autophagosome membranes [38–40], which are further matured by the
ATG14/beclin1/VPS34 complex [41,42]. ULK1 and beclin1 complexes are positively regu-
lated by the cofactor AMBRA1, which is required for their regulative ubiquitination [43,44].
In mammals, the autophagy conjugation machinery then regulates the lipidation of ATG8
proteins (mATG8) [34,45]. Each of the core components of the endosomal sorting complexes
required for transport (ESCRT) and machinery (ESCRT complex 0-III) are necessary for the
full maturation and sealing of the autophagosome [46,47], onto which syntaxin-17 (STX17),
an autophagosomal SNARE protein, is recruited [48] with the assistance of mATG8s
and autophagy factor IRGM [49]. STX17 regulates, together with other proteins such as
Vesicle-Associated Membrane Protein 8 (VAMP8) and synaptosomal-associated protein 29
(SNAP29), the fusion of the autophagosome with the lysosome [48]. Notably, mammalian
STX17 also contributes to the first steps of autophagosome formation downstream of
TANK-binding kinase 1 (TBK1) activity, which feeds into the activation of cell defense [50].

Autophagy leads to cargo degradation irrespective of its identity. However, while
core components of the autophagic machinery (i.e., the ATG conjugation machinery)
are common to most routes, the autophagy of specific structures and cargoes exhibits
particularities in its regulation and the specific source of phagosome membranes: ER-
phagy (degradation of ER) [51], mitophagy (selective degradation of damaged mitochon-
dria) [52], pexophagy (autophagy of damaged peroxisomes) [53], ribophagy (degradation
of ribosomes) [54], nucleophagy (degradation of nuclear membranes) [55,56], xenophagy
(degradation of invading pathogens by autophagy) [57,58], or aggrephagy (autophagic
clearance of protein aggregates) [59] (Figure 2). Selective cargo autophagy generally re-
quires specific receptors, e.g., selective degradation of ER requires different receptors such
as FAM134B [51], CCPG1 [60], RTN3 [61], and TEX264 [62,63]. In contrast, mitophagy re-
quires NDP52, optineurin, and TAXBP1 as receptors [64] and p62 [65]. Certain receptors are
common to more than one autophagic route: for example, NDP52 and optineurin control
mitophagy [64] as well as xenophagy [66,67]. Route-specific regulators have also been de-
scribed, apart from cargo-specific receptors. Microautophagy involves invagination of the
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lysosomal membrane to capture cargo for degradation [68], and involves both components of the autophagic machinery, including the conjugation machinery [69], and sequestosome-like receptors (SLRs) [70]. LC3-associated phagocytosis (LAP) requires the autophagy conjugation machinery but is controlled by RUBICON [71–73], which is an inhibitor of conventional autophagy [42,74]. Similar to LAP, other non-canonical autophagy processes utilize ATG conjugation and do not require autophagy-initiation machinery [75–77]. While a major share of therapeutic strategies rely on intervening major core components and regulators (the focus of our section below), these relatively recent mechanisms are regarded as interesting future candidates for personalized therapy of specific disorders.

Figure 1. Main extracellular stimuli and intracellular pathways controlling TFEB activation. TFEB is the master transcriptional regulator of both autophagy and lysosomal components, responding to important biological pathways and cellular functions. TFEB translocation to the nucleus depends on its phosphorylation status. Various extracellular and intracellular stimuli including growth factor/nutrient abundance or deprivation and oxidative stress activate, among others, LLBK1/AMPK and/or mTOR signaling which control TFEB phosphorylation status. Once phosphorylated, TFEB is sequestered in the cytosol by 14-3-3 proteins. Conversely, during starvation TFEB is dephosphorylated by PPP3CB enabling its nuclear translocation.

Figure 2. Distinct autophagic routes. Depending on the specific structures and cargoes initiating autophagy, different autophagic routes have been elucidated.
3. mTOR Signaling: A Key Regulatory Node Curbing Autophagy

mTOR is a serine/threonine kinase which functions at the interface between nutrient sensing and different cellular processes leading to cell growth and proliferation [78]. Since its discovery, there has been a progressive understanding of the different pathways orchestrated by mTOR, unveiling its role as a central hub for cellular and organismal physiology in all eukaryotes [79].

mTOR is composed by two distinct protein complexes in metazoans, named mTORC1 and mTORC2. Although they share some core protein components, different accessory elements account for structural and functional differences in rapamycin sensitivity and substrate specificity. mTORC1 is mainly constituted by mTOR, the mammalian lethal with SEC13 protein 8 (mLST8) [80], and the regulatory-associated protein of mTOR, RAPTOR [81]. Its major substrates are eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and p70S6 kinase (S6K1), through which mTORC1 controls protein synthesis, nutrient uptake, and autophagy, all leading to positive regulation of cellular growth.

mTORC2 bears, instead of RAPTOR, the rapamycin-insensitive companion of mTOR (RICTOR) protein [82,83], which interacts and binds to MAPK-associated protein 1 (mSIN1) [84,85]. Members of the AGC kinase family (including AKT, SGK, and PKCα) are major mTORC2 substrates, through which it regulates cytoskeletal behavior as well as different pro-survival pathways, all impinging on cellular proliferation.

Although it is expressed in all tissues, from the point of view of its function as a nutrient sensor mTOR is probably most important in metabolically intensive locations, such as muscle, liver, or adipose tissue. After feeding, insulin, secreted by the pancreas, activates mTORC1 and mTORC2, promoting glucose uptake and storage in the form of glycogen in skeletal muscle [86] as well as amino-acid incorporation, leading to muscle growth. In contrast, fasting activates a catabolic program that induces autophagy, leading to protein degradation and liver gluconeogenesis. Several lines of evidence indicate that this balance between anabolism and catabolism is fundamentally regulated by mTOR [87,88]. Liver-specific RICTOR-knockout mice, for instance, show alterations in lipid storage and hyperglycemia as a result of systemic insulin resistance [89–91], indicating that mTOR signaling alterations contribute to the development of diabetes. Similarly, adipose-specific RAPTOR-knockout mice are resistant to diet-induced obesity and present low body weight [92,93], in accordance with the role of mTOR in lipid anabolism and adipose-tissue function, and whole-body homeostasis therein [94,95].

The dysregulation of mTOR signaling is frequent in tumors [96]. Aberrant activation of mTORC1 signaling, for instance, favors tumor growth by eliciting cancer cells to bypass metabolic checkpoints. Hyperactivation of mTORC2 signaling, on the other hand, boosts metastasis by supporting AKT-dependent cytoskeletal remodeling [97]. Despite its complexity, the role of mTOR in cancer has led to different therapeutic strategies, including ‘rapalogs’—rapamycin derivatives—which have shown efficacy in certain contexts [98]. Prolonged mTOR inhibition can however lead to reactivation of cancer growth [99,100], stressing the need for further research to better understand the multifaceted impact of mTOR signaling on cancer progression.

4. Transcriptional Control of the Autophagolysosomal Machinery: TFEB and Its Regulation

TFEB is a major transcription factor which regulates the transcription of genes involved in several biological pathways, and participates in important cellular functions, including autophagy [7], lysosomal biogenesis [101], lysosomal exocytosis [14], lipid metabolism [13], mitophagy [102], and mitochondrial biogenesis [12]. A major regulatory layer controlling TFEB nuclear translocation and activity is affected through phosphorylation, mainly controlled by the mTOR kinase [103,104], and by a phosphatase, PPP3CB [105] (Figure 1). mTOR phosphorylates the Ser211 residue of TFEB [104], eliciting its interaction with 14-3-3 proteins which sequester TFEB in the cytosol [104,105] (Figure 3). 14-3-3 proteins also interact with other members of the MiTF family [104,106,107]. Notably, TFEB interacts
TFEB can be phosphorylated by several kinases either dependent or independent of mTOR. Notably, only the mTORC1 complex can regulate TFEB activity through the phosphorylation of Ser122 and Ser211. Other kinases involved in the mTOR pathway may interact with TFEB. In particular, ERK1 determines Ser142 phosphorylation and subsequent TFEB cytoplasmic sequestration. GSK3β and Akt may regulate TFEB nuclear translocation in an mTOR-independent manner, phosphorylating Ser134–138 and Ser476, respectively. There are additional kinases which phosphorylate TFEB at other residues, contributing to the regulation of its nuclear translocation [110]. Indeed, TFEB is phosphorylated by ERK at Ser-142 residue, also blocking its nuclear translocation [101]. In contrast, TFEB phosphorylation at Ser138 controls its nuclear export [110,111].

Other kinases independent from mTOR have been implicated in TFEB nuclear translocation and in the regulation of the lysosome system [110]. PKC, for instance, controls nuclear translocation of TFEB in an mTOR-independent manner [112]; GSK3β phosphorylates TFEB at Ser134 and Ser138, which, like mTOR phosphorylation, keeps TFEB in the cytosol [112]; AKT phosphorylates TFEB at its Ser467 residue, thus blocking its translocation to the nucleus [113]. TFEB is dephosphorylated by a calcineurin phosphatase, PPP3CB, during starvation. PPP3CB dephosphorylates phosphor-Ser211 TFEB [104], releasing it from 14-3-3 proteins and eliciting its nuclear translocation [105]. The relevance of TFEB for cell homeostasis is further highlighted by the increasing number of additional posttranslational modifications recently described (acetylation, SUMOylation) [114,115], reflecting the integration of several inputs feeding on this central node regulating autophagy and lysosomal function. Finally, TFEB expression is sensitive to different cues challenging cell homeostasis; examples are ER
stress, which can promote TFEB upregulation to engage autophagy and ensure lysosomal function downstream with the Unfolded Protein Response (UPR) effectors XBP1 and PERK/ATF4 [116–118], and oxidative stress, which induces TFEB nuclear translocation in an NRF2-dependent manner [117].

5. TFEB and Autophagy

Current models propose that TFEB operates upstream of the autophagy pathway [1,7,13,119]. TFEB positively correlates with gene expression changes in autophagy genes and relative lipidation of the autophagy marker LC3 [7]. TFEB controls autophagy during different stresses including starvation [7], lysosomal damage [120], neuronal toxicity [121,122] inflammation [123–126], and infection with pathogens [127–130]. Recent evidence suggests that TFEB and TFE3 control ERphagy [131] by regulating the expression of the ERphagy receptor FAM134B [51].

Notably, recent reports indicate that autophagy may in turn operate upstream of TFEB to control its nuclear translocation during bulk and selective autophagy [102,132]. Mammalian ATG8 proteins (mATG8s), which are involved in autophagosome elongation [133,134] and autophagosome–lysosome fusion [133,135], also participate in lysosomal biogenesis [136]. mATG8s form complexes with autophagy factor IRGM and SNARE protein Stx17 [49]. Like mATG8s, Stx17 [48,50] and IRGM [137,138] participate in different steps of autophagy. This complex consisting of IRGM, Stx17, and mATG8s [49] controls TFEB nuclear translocation in response to starvation. IRGM and GABARAP (a member of mATG8s family) directly interact with TFEB. IRGM, Stx17, and mAtg8s proteins influence TFEB nuclear translocation by inhibiting mTOR activity in response to amino-acid starvation [132]. mATG8 proteins also control TFEB action at transcriptional level [132]. While mTOR-dependent TFEB phosphorylation leads to TFEB cytosolic retention [103–105], IRGM-dependent dephosphorylation favors its nuclear translocation [132]. Therefore, there is a positive feedback loop between autophagy and the lysosomal system to regulate cellular homeostasis.

6. TFEB in Lysosomal Biogenesis and Function

Lysosomes are crucial components of the cellular degradation and recycling system. Lysosomes contain approximately 60 different soluble hydrolitic enzymes, which are directly involved in the degradation of macromolecules in other cellular wastes [11]. TFEB is a master regulator of lysosomal biogenesis [101,119,139]. TFEB transcriptionally regulates the gene expression of the CLEAR (coordinated lysosomal expression and regulation) network, the expression of target genes bearing the CLEAR motif, thereby modulating autophagy and lysosomal biogenesis [119,139]. TFEB not only controls lysosomal biogenesis but also other processes associated with lysosomal function such as autophagy [7], endocytosis [140], and lysosomal exocytosis [14]. An additional role for the lysosomal system pertains to the link between membrane trafficking, ER architecture, and mTORC1 activation status [141–143]; the tight control of such a central node for lysosomal regulation by mTORC1 reflects the functional coupling of these cellular systems.

7. The Autophagolysosomal System and Cellular ROS Homeostasis

The term “Reactive Oxygen Species” (ROS) is used for a heterogeneous group of highly reactive chemical entities containing molecular oxygen—including oxygen radicals (i.e., superoxide (O2•−), and hydroxyl (•OH), peroxyl (RO2•), and alkoxyl (RO•) radicals), and non-radicals (i.e., hypochlorous acid (HClO), singlet oxygen (1O2), and hydrogen peroxide (H2O2). Most, if not all of them, are typically by-products of cell metabolism, even under physiological conditions [144,145], although different external agents such as xenotoxins or ionizing radiations can provoke extensive oxidative stress and ROS accumulation [146,147]. Cells have evolved intricate antioxidant systems to curb damaging rises in ROS levels, such as glutathione pair (GSSG/GSH), nicotinamide adenine dinucleotide pair (NADH/NAD+), superoxide dismutases (SODs), catalase, glutathione peroxidases
(GPXs), peroxiredoxins (PRXs), or thioredoxins (TRXs) [148–150]. These are integrated in different stress responses (UPR, electrophilic-stress response, integrated-stress response, AMPK network) [151–155], triggered by stimuli (nutrient deficiency, metabolic imbalance, lipotoxicity, and proteotoxicity) that can potentially boost ROS accumulation.

Of note, autophagy is commonly considered as an additional branch of these stress networks, and is activated by many of these adverse conditions both through direct links, as well as though the general integration of the mTOR signaling network with these stress pathways [156,157]. Autophagy is an important contributor to cell survival from ROS-inducing stress, by curbing the accumulation of damaged structures and removing faulty organelles acting as sources of ROS [158].

The relevance of this link between ROS production and autophagy is exemplified by the fact that elevated ROS species and/or compromised antioxidant responses are frequent hallmarks of the altered metabolism and environment of tumor cells, often actively promoting tumorigenesis [159–161]. These features are both considered appealing therapeutic targets per se, and opportunities for synergistic interventions. Two emerging, related therapeutic strategies based on these phenotypic alterations of tumor cells are the use of ascorbate (for which certain tumor cells, such as glioblastomas, exhibit paradoxical differential toxicity through oxidative damage) [162,163] and other strategies leveraging on mechanisms driving ferroptosis, a specific cell-death program triggered by iron-dependent accumulation of peroxidized lipid species [164–166]. Autophagy can frequently act as a pro-survival response counteracting these damaging stimuli in different types of tumors [167,168]. However, autophagy itself can be both positively or negatively modulated by these forms of oxidative stress, and may serve as part of the effector mechanism of the ferroptotic cascade [162,169–172]. Further research is thus warranted to understand the architecture of the underlying networks and the principles of their functioning.

8. Modulating the Autophagolysosomal System in Cancer: Therapeutic Opportunities

Autophagy induction by cancer-associated stimuli (oxidative stress, suboptimal nutrient supply, and hypoxia), and its tight relationship with pro-survival cell pathways, support a direct role of autophagy in cancer transformation. However, the role of autophagy in cancer is highly contextual. Autophagy can act both as a tumor suppressor mechanism, favoring the elimination of damaged proteins or organelles, or as tumorigenic, providing a source of nutrients and energy to tumor cells and further favoring their transformation. Murine models demonstrate that autophagic gene deficiency favors tumorigenesis, at least at initial stages [173]. Deficiency of autophagic genes such as Beclin1 or Atg5 has been found in various cancers, including hepatocellular carcinoma (HCC), breast, ovarian, and prostate cancer [173,174]. Impaired autophagy can promote a tumorigenic environment through ROS dysregulation and chronic induction of inflammatory states [175]. Autophagy defects in mice cause accumulation of p62 aggregates, oxidative stress, and p62-dependent hepatocyte cell death favoring hepatocarcinoma progression [176,177]. In breast cancer, aberrantly expressed p62 may favor the generation of breast stem cells (CSCs) through the induction of MYC oncogene [178].

On the other hand, at advanced cancer stages, increased autophagy can sustain tumor cell growth in the nutrient-deficient, hypoxic tumor microenvironment, and favor chemoresistance by counteracting the damage of cell structures [179]. Further, autophagy promotes resistance to anoikis (a form of cell death induced by cellular detachment from the extracellular matrix) in gliomas, enabling tumor spreading and metastasis [180,181]. However, autophagy inhibition can also favor tumor cell invasiveness through the induction of dedifferentiated, basal phenotypes in breast cancer [182]. Upregulation of autophagy induction confers chemoresistance [20,179,183] and promotes the maintenance and survival of CSCs in different cancers including breast, pancreas, liver, ovarian cancer, osteosarcoma, and glioblastoma [184].

Cancer cells generally grow faster than non-transformed counterparts and have high metabolic demands, so they may use autophagy and the lysosomal pathway to meet high
demands for energy and anabolic flux [28]. In fact, similar cancers bearing different genetic mutations may vary for their dependence on autophagy. For instance, tumors with mutations in the RAS–MAPK pathway, such as central nervous system (CNS) tumors bearing a BRAF V600E mutation, but not their wild-type BRAF-expressing counterparts, were found to be strongly dependent on autophagy [19,185]. This discovery paves the way to the translational employ of autophagy inhibition in combination with other therapeutic strategies.

Due to the relevance of autophagy and the lysosome system in cancer biology, their modulation by drugs is a current target in cancer therapy [186,187].

To this purpose, multiple steps in autophagy are currently being considered. Inhibition of ULK1 sensitizes cancer cell to nutrient stress [188] and mTOR inhibitors [189]; inhibition of VSP34 has shown to improve the effect of mTOR inhibition and tyrosine-kinase inhibitor on suppression of cancer growth [190,191]; inhibition of ATG4B, a protease that controls lipidation and delipidation of mATG8s [192], also suppresses cancer progression [193]. Chloroquine and its derivative hydroxychloroquine are lysosomotropic agents which inhibit fusion of autophagosomes with lysosomes [194], and are at different stages of clinical trials against different types of cancers [20,24].

Lysosomes are nutrient-sensing organelles. Lysosomes and their related biological functions, such as endocytosis, phagocytosis, and micropinocytosis, are involved in maintaining energetics in cancer [22]. Lysosomal volume and subcellular localization are changed during cancerous transformation [195]. Lysosomal hydrolases such as cathepsin are upregulated and display altered localization in cancer. Increased cathepsin expression is correlated with cancer progression [196,197]. Lysosomal membrane protein LAMP1 is associated with cancer development and progression [22,198]. Lysosomal V-ATPase has been shown to affect tumor microenvironment [199].

Due to its prominent role as an upstream regulator of autophagy and lysosomal function, TFEB might constitute a priority target for the efficient therapeutic intervention of these routes. RNA-based therapeutics are expected to soar after the success of RNA-based vaccines; in this sense, numerous studies indicate TFEB is an effective target for the modulation of autophagy and lysosomal activity to successfully counteract different pathological conditions, including cancer [200–204]. Reflecting the highly contextual role of autophagy in cancer, while TFEB and related factors have frequently been regarded as oncogenes, TFEB can behave as a tumor suppressor, as recently reported for acute myeloid leukemia (AML) [205]. It must be noted that effective reversion of certain pathological conditions through TFEB modulation may require the simultaneous intervention of associated gene-expression networks, such as those controlled by YAP [206]. Notably, small compounds amenable for human therapeutics such as genistein, 20-deoxyxgenol, curcumin, or betulinic acid have been reported to be capable of enhancing TFEB-dependent lysosomal activity [207–210]; other TFEB-modulating compounds were identified in phenotypic screens in Caenorhabditis elegans [211]. The synergistic potential of these compounds with other treatments sensitizing tumor cells to autophagic modulation deserves further exploration.

9. Nanomedicine May Increase the Potential of Drugs Modulating Autophagy

As described in the previous section, autophagy may play a dual role in cancer depending on cell type and stage, potentially acting both as tumor suppressor and as a promoter of tumor progression [212]. For this reason, both the inhibition of autophagy and its overstimulation are strategies under assessment to counteract cancer, and several drugs, such as hydroxychloroquine (HCQ), 3-methyl-adenine (3-MA), and everolimus, have been approved by the Food and Drug Administration (FDA) and are currently employed in clinics in combination with other chemotherapeutic regimens [179,213].

However, these treatments present a variety of adverse effects such as low specificity, irregular distribution in the body, and rapid drug clearance [214]. For this reason, novel approaches aimed at modulating autophagy are warranted. Recent advances in nanotechnology offer many tools to counteract cancer with innovative and smart therapeutic agents by overcoming obstacles frequently encountered
with standard chemothterapeutics. Novel smart nanomaterials have been engineered that, depending on their chemical–physical proprieties, can be divided into various categories, such as liposomes, polymers, metals, and metal-oxide nanoparticles (NPs) [215]. Most of these nanomaterials are used as nanocarriers to deliver therapeutic molecules such as drugs, proteins, or nucleic acids into specific target sites without affecting healthy tissues [216,217]. In this regard, it must be noted that a major advantage of such an approach consists in the fact that nanocarriers can accumulate in the leaky tumor vasculature, a process known as enhanced permeability and retention effect (EPR). This capability is essential in guaranteeing specificity of the therapeutic system and for its applications in vivo [218]. Moreover, nanocarriers can release their therapeutic cargo in a stable and controlled manner. A plethora of stimuli, such as changes in pH, redox, temperature, or magnetic forces, can trigger the release of drugs by evoking a change in the structures of the nanocomplex, to ensure toxicity exclusively into target tissue, without affecting healthy tissues [219].

Combination therapy with cisplatin and chloroquine in micelles formed by self-assembling hybrid dendritic-linear-dendritic block copolymers (HDLDBCs) increased cytotoxicity in tumor cells while maintaining a low degree of cytotoxicity against non-tumor cells [220]. Lys-05, an autophagy inhibitor which accumulates within and deacidifies the lysosome [221], was hybridized with a lysosomotropic detergent (MSDH) to produce nanoassemblies. The resulting nanoparticles were demonstrated to have excellent pharmacokinetic and toxicological profiles and a dramatic efficacy against tumors in vivo [222].

The surface of gold nanoparticles (Au-NPs) can be easily functionalized with chemotherapeutics or nucleic acids, such as snake-venom-protein toxin NKCT1, monoclonal antibodies, or quercetin, making them excellent autophagy inducers for cancer therapy [223–225].

Besides acting as nano-carriers, nanoparticles of specific materials may have the intrinsic ability of altering the complex network of signaling pathways and molecules involved in autophagy regulation, and thus represent an exciting therapeutic approach against different human tumors [226]. Bare iron-oxide NPs are significantly cytotoxic to human lung carcinoma cells (A549 cells), causing ROS-induced autophagy and subsequent cell death, but not to normal human-lung fibroblast cells [227]. Chiral nanomaterials are being developed to modulate autophagy activity in tumors [228], and chiral polymer-modified nanoparticles may induce autophagy-mediated tumor suppression in vivo [229]. Moreover, D- and L-cysteine-modified Cu$_2$xS nanocrystals (NCs) were reported to produce large amounts of ROS in tumor cells, promoting cellular autophagy [230].

The use of modified NPs to intervene in autophagy is not limited to cancer, and many other diseases can be treated by this approach. Indeed, defective clearance of misfolded proteins and/or damaged organelles occurs in a plethora of human diseases, such as muscular or neurodegenerative diseases, and the pharmacological modulation of this process may represent a valid therapeutic approach. For example, cerium oxide nanoparticles (CeO$_2$-NPs) were reported to activate autophagy and promote clearance of autophagic cargo, thus exerting neuroprotection. [231]. Furthermore, europium hydroxide nanoparticles [(EuIII(OH)3)-NPs] have been shown to stimulate autophagy flux, reducing mutant-huntingtin-protein aggregation [232].

However, despite such promising potential, the autophagy induction activity of these nanomaterials can also lead to cardiovascular, respiratory, and immune-system toxicity [233]. Hence, the use of nanomedicines in autophagy modulation is at its infancy and the clinical translation of the results thus far obtained is still a challenge [234].

In conclusion, further effort is needed to understand the molecular mechanisms and principles governing the autophagolysosomal system, for its efficient, safe, and personalized intervention across multiple diseases, including cancer.

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References

1. Ballabio, A.; Bonifacino, J.S. Lysosomes as dynamic regulators of cell and organismal homeostasis. Nat. Rev. Mol. Cell Biol. 2020, 21, 101–118. [CrossRef]
2. Perera, R.M.; Zoncu, R. The Lysosome as a Regulatory Hub. Annu. Rev. Cell Dev. Biol. 2016, 32, 223–253. [CrossRef]
3. Xu, H.; Ren, D. Lysosomal physiology. Annu. Rev. Physiol. 2015, 77, 57–80. [CrossRef]
4. Levine, B.; Kroemer, G. Biological Functions of Autophagy Genes: A Disease Perspective. Cell 2019, 176, 11–42. [CrossRef][PubMed]
5. Dikic, I.; Elazar, Z. Mechanism and medical implications of mammalian autophagy. Nat. Rev. Mol. Cell Biol. 2018, 19, 349–364. [CrossRef][PubMed]
6. Steingrimsson, E.; Copeland, N.G.; Jenkins, N.A. Melanocytes and the microphthalmia transcription factor network. Annu. Rev. Genet. 2004, 38, 365–411. [CrossRef][PubMed]
7. Settembre, C.; Di Malta, C.; Polito, V.A.; García Arencibia, M.; Vetrini, F.; Erdin, S.; Erdin, S.U.; Huynh, T.; Medina, D.; Colella, P.; et al. TFEB links autophagy to lysosomal biogenesis. Science 2011, 332, 1429–1433. [CrossRef]
8. Cunningham, K.M.; Maulding, K.; Ruan, K.; Senturk, M.; Grima, J.C.; Sung, H.; Zuo, Z.; Song, H.; Gao, J.; Dubey, S.; et al. TFEB/Mitf links impaired nuclear import to autophagolysosomal dysfunction in C9-ALS. eLife 2019, 9, e59419. [CrossRef]
9. Yang, M.; Liu, E.; Tang, L.; Lei, Y.; Sun, X.; Hu, J.; Dong, H.; Yang, S.M.; Gao, M.; Tang, B. Emerging roles and regulation of Mit/TFE transcriptional factors. Cell Commun. Signal. 2018, 16, 31. [CrossRef]
10. Moller, K.; Sigurbjornsdottir, S.; Armani, A.; Viscomi, C.; D’Orsi, L.; De Cegli, R.; Polishchuk, E.V.; Lamperti, C.; Di Meo, I.; Romanello, V.; Marchet, S.; et al. Transcription Factor EB Controls Metabolic Flexibility during Exercise. Cell Metab. 2017, 25, 182–196. [CrossRef]
11. Napolitano, G.; Ballabio, A. TFEB at a glance. J. Cell Sci. 2016, 129, 2475–2481. [CrossRef]
12. Mansueto, G.; Armani, A.; Viscomi, C.; D’Orsi, L.; De Cegli, R.; Polichshuk, E.V.; Lamperti, C.; Di Meo, I.; Romanello, V.; Marchet, S.; et al. Transcription Factor EB Controls Metabolic Flexibility during Exercise. Cell Metab. 2017, 25, 182–196. [CrossRef]
13. Settembre, C.; De Cegli, R.; Mansueto, G.; Saha, P.K.; Vetrini, F.; Visvikis, O.; Huynh, T.; Carissimo, A.; Palmer, D.; Klisch, T.J.; et al. TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. Nat. Cell Biol. 2013, 15, 647–658. [CrossRef][PubMed]
14. Medina, D.L.; Fraldi, A.; Bouche, V.; Annunziata, F.; Mansueto, G.; Spamanato, C.; Puri, C.; Pignata, A.; Martinas, J.A.; Sardiello, M.; et al. Transcriptional activation of lysosomal exocytosis promotes cellular clearance. Dev. Cell 2011, 21, 421–430. [CrossRef][PubMed]
15. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. CA Cancer J. Clin. 2020, 70, 7–30. [CrossRef][PubMed]
16. Clara, J.A.; Monge, C.; Yang, Y.; Takebe, N. Targeting signalling pathways and the immune microenvironment of cancer stem cells—A clinical update. Nat. Rev. Clin. Oncol. 2020, 17, 204–232. [CrossRef]
17. Sanchez-Vega, F.; Mina, M.; Armenia, J.; Chatila, W.K.; Luna, A.; La, K.C.; Dimitriadiy, S.; Liu, D.L.; Kantheti, H.S.; Saghatfina, S.; et al. Oncogenic Signaling Pathways in The Cancer Genome Atlas. Cell 2018, 173, 321–337.e310. [CrossRef][PubMed]
18. Sever, R.; Brugge, J.S. Signal transduction in cancer. Cold Spring Harb. Perspect. Med. 2015, 5, a006098. [CrossRef][PubMed]
19. Mulcahy Levy, J.M.; Thorburn, A. Autophagy in cancer: Moving from understanding mechanism to improving therapy responses in patients. Cell Death Differ. 2020, 27, 843–857. [CrossRef]
20. Levy, J.M.M.; Towers, C.G.; Thorburn, A. Targeting autophagy in cancer. Nat. Rev. Cancer 2017, 17, 528–542. [CrossRef]
21. Amaravadi, R.K.; Lippincott-Schwartz, J.; Yin, X.M.; Weiss, W.A.; Takebe, N.; Timmer, W.; D’Paola, R.S.; Lotze, M.T.; White, E. Principles and current strategies for targeting autophagy for cancer treatment. Clin. Cancer Res. 2011, 17, 654–666. [CrossRef]
22. Fennelly, C.; Amaravadi, R.K. Lysosomal Biology in Cancer. *Methods Mol. Biol.* 2017, 1594, 293–308. [CrossRef] [PubMed]

23. Amaravadi, R.; Kimmelman, A.C.; White, E. Recent insights into the function of autophagy in cancer. *Genes Dev.* 2016, 30, 1913–1930. [CrossRef] [PubMed]

24. Amaravadi, R.K.; Kimmelman, A.C.; Debnath, J. Targeting Autophagy in Cancer: Recent Advances and Future Directions. *Cancer Discov.* 2019, 9, 1167–1181. [CrossRef] [PubMed]

25. Manic, G.; Obrist, F.; Kroemer, G.; Vitale, I.; Galluzzi, L. Chloroquine and hydroxychloroquine for cancer therapy. *Mol. Cell Oncol.* 2014, 1, e29911. [CrossRef] [PubMed]

26. Xu, R.; Ji, Z.; Xu, C.; Zhu, J. The clinical value of using chloroquine or hydroxychloroquine as autophagy inhibitors in the treatment of cancers: A systematic review and meta-analysis. *Medicine* 2018, 97, e12992. [CrossRef] [PubMed]

27. Davis, I.J.; Kim, J.J.; Ozsolak, F.; Widlund, H.R.; Rozenblatt-Rosen, O.; Granter, S.R.; Du, J.; Fletcher, J.A.; Denny, C.T.; Lessnick, S.L.; et al. Oncogenic MITF dysregulation in clear cell sarcoma: Defining the MIT family of human cancers. *Cancer Cell* 2006, 9, 473–484. [CrossRef] [PubMed]

28. Perera, R.M.; Di Malta, C.; Ballabio, A. MiT/TFE Family of Transcription Factors, Lysosomes, and Cancer. *Annu. Rev. Cancer Biol.* 2019, 3, 203–222. [CrossRef]

29. Di Malta, C.; Siciliano, D.; Calcagni, A.; Monfregola, J.; Punzi, S.; Pastore, N.; Eastes, A.N.; Davis, O.; De Cegli, R.; Zampelli, A.; et al. Transcriptional activation of RagD GTPase controls mTORC1 and promotes cancer growth. *Science* 2017, 356, 1188–1192. [CrossRef]

30. Kim, J.; Kundu, M.; Viollet, B.; Guan, K.L. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat. Cell Biol.* 2011, 13, 132–141. [CrossRef]

31. Inoki, K.; Kim, J.; Guan, K.L. AMPK and mTOR in cellular energy homeostasis and drug targets. *Annu. Rev. Pharm. Toxicol.* 2012, 52, 381–400. [CrossRef]

32. Hara, T.; Takamura, A.; Kishi, C.; Iemura, S.; Natsume, T.; Guan, J.L.; Mizushima, N. FIP200, a ULK-interacting protein, is required for autophagosome formation in mammalian cells. *J. Cell Biol.* 2008, 181, 497–510. [CrossRef]

33. Hosokawa, N.; Hara, T.; Kaizuka, T.; Kishi, C.; Takamura, A.; Miura, Y.; Iemura, S.; Natsume, T.; Takehana, K.; Yamada, N.; et al. Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. *Mol. Biol. Cell* 2009, 20, 1981–1991. [CrossRef]

34. Mizushima, N.; Yoshimori, T.; Ohsumi, Y. The role of Atg proteins in autophagosome formation. *Annu. Rev. Cell Dev. Biol.* 2011, 27, 107–132. [CrossRef]

35. Kim, J.; Kim, Y.C.; Fang, C.; Russell, R.C.; Kim, J.H.; Fan, W.; Liu, R.; Zhong, Q.; Guan, K.L. Differential regulation of distinct Vps34 complexes by AMPK in nutrient stress and autophagy. *Cell* 2013, 152, 290–303. [CrossRef]

36. Vescovo, T.; Pagni, B.; Piacentini, M.; Fimia, G.M.; Antonioli, M. Regulation of Autophagy in Cells Infected With Oncogenic Human Viruses and Its Impact on Cancer Development. *Front. Cell Dev. Biol.* 2020, 8, 47. [CrossRef]

37. Deretic, V.; Saitoh, T.; Akira, S. Autophagy in infection, inflammation and immunity. *Nat. Rev. Immunol.* 2013, 13, 722–737. [CrossRef]

38. Osawa, T.; Kotani, T.; Kawaoka, T.; Hirata, E.; Suzuki, K.; Nakatogawa, H.; Ohsumi, Y.; Noda, N.N. Atg2 mediates direct lipid transfer between membranes for autophagosome formation. *Nat. Struct. Mol. Biol.* 2019, 26, 281–288. [CrossRef] [PubMed]

39. Gomez-Sanchez, R.; Rose, J.; Guimaraes, R.; Mari, M.; Papinski, D.; Rieter, E.; Geerts, W.J.; Hardenberg, R.; Kraft, C.; Ungermann, C.; et al. Atg9 establishes Atg2-dependent contact sites between the endoplasmic reticulum and phagosomes. *J. Cell Biol.* 2018, 217, 2743–2763. [CrossRef] [PubMed]

40. Matoba, K.; Kotani, T.; Tsutsumi, A.; Tsuji, T.; Mori, T.; Noshido, D.; Sugita, Y.; Nomura, Y.; Iwata, S.; Ohsumi, Y.; et al. Atg9 is a lipid scramblase that mediates autophagosomal membrane expansion. *Nat. Struct. Mol. Biol.* 2020, 27, 1185–1193. [CrossRef] [PubMed]

41. Itakura, E.; Kishi, C.; Inoue, K.; Mizushima, N. Beclin 1 forms two distinct phosphatidylinositol 3-kinase complexes with mammalian Atg14 and UVRAG. *Mol. Biol. Cell* 2008, 19, 5360–5372. [CrossRef]

42. Matsunaga, K.; Saitoh, T.; Tabata, K.; Omori, H.; Sato, T.; Kurotani, N.; Maejima, I.; Shirahama-Noda, K.; Ichimura, T.; Isobe, T.; et al. Two Beclin 1-binding proteins, Atg14L and Rubicon, reciprocally regulate autophagy at different stages. *Nat. Cell Biol.* 2009, 11, 385–396. [CrossRef]

43. Nazio, F.; Strappazzon, F.; Antonioli, M.; Bielli, P.; Cianfanelli, V.; Bordi, M.; Gretzmeier, C.; Dengiel, J.; Piacentini, M.; Fimia, G.M.; et al. mTOR inhibits autophagy by controlling ULK1 ubiquitylation, self-association and function through AMBRA1 and TRAF6. *Nat. Cell Biol.* 2013, 15, 406–416. [CrossRef] [PubMed]

44. Antonioli, M.; Albiero, F.; Fimia, G.M.; Piacentini, M. AMBRA1-regulated autophagy in vertebrate development. *Int. J. Dev. Biol.* 2015, 59, 109–117. [CrossRef] [PubMed]

45. Mizushima, N. The ATG conjugation systems in autophagy. *Curr. Opin. Cell Biol.* 2020, 63, 1–10. [CrossRef]

46. Takahashi, Y.; He, H.; Tang, Z.; Hattori, T.; Liu, Y.; Young, M.M.; Serfass, J.M.; Chen, L.; Gebru, M.; Chen, C.; et al. An autophagy assay reveals the ESCRT-III component CHMP2A as a regulator of phagophore closure. *Nat. Commun.* 2018, 9, 2855. [CrossRef]

47. Zhou, F.; Wu, Z.; Zhao, M.; Murtazina, R.; Cai, J.; Zhang, A.; Li, R.; Sun, D.; Li, W.; Zhao, L.; et al. Rab5-dependent autophagosome closure by ESCRT. *J. Cell Biol.* 2019, 218, 1908–1927. [CrossRef] [PubMed]

48. Itakura, E.; Kishi-Itakura, C.; Mizushima, N. The hairpin-type tail-anchored SNARE syntaxin 17 targets to autophagosomes for fusion with endosomes/lysosomes. *Cell* 2012, 151, 1256–1269. [CrossRef]
77. Fletcher, K.; Ulferts, R.; Jacquin, E.; Veith, T.; Gammoh, N.; Arasteh, J.M.; Mayer, U.; Carding, S.R.; Wileman, T.; Beale, R.; et al. The WD40 domain of ATG16L1 is required for its non-canonical role in lipidation of LC3 at single membranes. EMBO J. 2018, 37, e97840. [CrossRef]

78. Laplante, M.; Sabatini, D.M. mTOR signaling in growth control and disease. Cell 2012, 149, 274–293. [CrossRef]

79. Vezina, C.; Kudelski, A.; Sehgal, S.N. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. J. Antibiot. 1975, 28, 721–726. [CrossRef]

80. Kim, D.H.; Sarbassov, D.D.; Ali, S.M.; Latek, R.R.; Guntur, K.V.; Erdjument-Bromage, H.; Tempst, P.; Sabatini, D.M. GbetaL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. Mol. Cell 2003, 11, 895–904. [CrossRef]

81. Kim, D.H.; Sarbassov, D.D.; Ali, S.M.; King, J.E.; Latek, R.R.; Erdjument-Bromage, H.; Tempst, P.; Sabatini, D.M. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell 2002, 110, 163–175. [CrossRef]

82. Sarbassov, D.D.; Ali, S.M.; Kim, D.H.; Guertin, D.A.; Latek, R.R.; Erdjument-Bromage, H.; Tempst, P.; Sabatini, D.M. Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton. Curr. Biol. 2004, 14, 1296–1302. [CrossRef] [PubMed]

83. Jacinto, E.; Loewith, R.; Schmidt, A.; Lin, S.; Ruegg, M.A.; Hall, A.; Hall, M.N. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. Nat. Cell Biol. 2004, 6, 1122–1128. [CrossRef]

84. Frias, M.A.; Thorzen, C.C.; Jaffe, J.D.; Schroder, W.; Scuilett, T.; Carr, S.A.; Sabatini, D.M. mSin1 is necessary for Akt/PKB phosphorylation, and its isoforms define three distinct mTORCs. Curr. Biol. 2006, 16, 1865–1870. [CrossRef] [PubMed]

85. Jacinto, E.; Facchinetti, V.; Liu, D.; Soto, N.; Wei, S.; Jung, S.Y.; Huang, Q.; Qin, J.; Su, B. SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. Cell 2006, 127, 125–137. [CrossRef] [PubMed]

86. Cross, D.A.; Alessi, D.R.; Cohen, P.; Andjelkovich, M.; Hemmings, B.A. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature 1995, 378, 785–789. [CrossRef] [PubMed]

87. Sengupta, S.; Peterson, T.R.; Laplante, M.; Oh, S.; Sabatini, D.M. mTORC1 controls fasting-induced ketogenesis and its modulation by ageing. Nature 2010, 468, 1100–1104. [CrossRef]

88. Komatsu, M.; Waguri, S.; Ueno, T.; Iwata, J.; Murata, S.; Tanida, I.; Ezaki, J.; Mizushima, N.; Ohsumi, Y.; Uchiyama, Y.; et al. The WD40 domain of ATG16L1 is required for its non-canonical role in lipidation of LC3 at single membranes. EMBO J. 2018, 37, e97840. [CrossRef]

89. Polak, P.; Cybulski, N.; Feige, J.N.; Auwerx, J.; Ruegg, M.A.; Hall, M.N. Adipose-specific knockout of raptor results in lean mice with enhanced mitochondrial respiration. Cell Metab. 2008, 8, 399–410. [CrossRef]

90. Lee, S.J.; Diener, K.; Kaufman, S.; Krieger, J.P.; Pettersen, K.G.; Jejelava, N.; Arnold, M.; Watts, A.G.; Langhans, W. Limiting glucocorticoid secretion increases the anorexigenic property of Exendin-4. Mol. Metab. 2016, 5, 552–565. [CrossRef] [PubMed]

91. Yuan, M.; Pino, E.; Wu, L.; Kacergis, M.; Soukas, A.A. Identification of Akt-independent regulation of hepatic lipogenesis by mammalian target of rapamycin (mTOR) complex 2. J. Biol. Chem. 2012, 287, 29579–29588. [CrossRef]

92. Laplante, M.; Sabatini, D.M. mTOR signaling in growth control and disease. Cell Metab. 2008, 8, 224–236. [CrossRef] [PubMed]

93. Sengupta, S.; Peterson, T.R.; Laplante, M.; Oh, S.; Sabatini, D.M. mTORC1 controls fasting-induced ketogenesis and its modulation by ageing. Nature 2010, 468, 1100–1104. [CrossRef]

94. Kim, D.H.; Sarbassov, D.D.; Ali, S.M.; Latek, R.R.; Erdjument-Bromage, H.; Tempst, P.; Sabatini, D.M. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell 2002, 110, 163–175. [CrossRef]

95. Porstmann, T.; Santos, C.R.; Griffiths, B.; Cully, M.; Wu, M.; Leevers, S.; Griffiths, J.R.; Chung, Y.L.; Schulze, A. SREBP activity is regulated by mTORC2/RICTOR Impairs Melanoma Hepatic Metastasis. Cancer Discov. 2014, 5, 125–137. [CrossRef] [PubMed]

96. Hagiwara, A.; Cornu, M.; Cybulski, N.; Polak, P.; Betz, C.; Trapani, F.; Terracciano, L.; Heim, M.H.; Ruegg, M.A.; Hall, M.N. Hepatic mTORC2 activates glycolysis and lipogenesis through Akt, glucokinase, and SREBP1c. Cell Metab. 2012, 15, 725–738. [CrossRef]

97. Menon, S.; Manning, B.D. Common corruption of the mTOR signaling network in human tumors. Oncogene 2008, 27 (Suppl. 2), S43–S51. [CrossRef]

98. Schmidt, K.M.; Dietrich, P.; Hackl, C.; Guenzle, J.; Bronsert, P.; Wagner, C.; Fichtner-Feigl, S.; Schlitt, H.J.; Geissler, E.K.; Hellerbrand, C.; et al. Inhibition of mTORC2/RICTOR Impairs Melanoma Hepatic Metastasis. Neoplasia 2018, 20, 1198–1208. [CrossRef] [PubMed]

99. Wagle, N.; Van Allen, E.M.; Treacy, D.J.; Frederick, D.T.; Cooper, Z.A.; Taylor-Weiner, A.; Rosenberg, M.; Goetz, E.M.; Sullivan, R.J.; Farlow, D.N.; et al. MAP kinase pathway alterations in BRAF-mutant melanoma patients with acquired resistance to combined RAF/MEK inhibition. Cancer Discov. 2014, 4, 61–68. [CrossRef] [PubMed]

100. Sardiello, M.; Palmieri, M.; di Ronza, A.; Medina, D.L.; Valenza, M.; Gennarino, V.A.; Di Malta, C.; Donaudi, F.; Embrione, V.; Polishchuk, R.S.; et al. A gene network regulating lysosomal biogenesis and function. Science 2009, 325, 473–477. [CrossRef]
102. Nezich, C.L.; Wang, C.; Fogel, A.I.; Youle, R.J. Mit/TFE transcription factors are activated during mitophagy downstream of Parkin and Atg5. J. Cell Biol. 2015, 210, 435–450. [CrossRef] [PubMed]

103. Settembre, C.; Zoncu, R.; Medina, D.L.; Vetriani, F.; Erdin, S.; Huynh, T.; Ferron, M.; Karsenty, G.; Vellard, M.C.; Facchinetti, V.; et al. A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFE3. EMBO J. 2012, 31, 1095–1108. [CrossRef] [PubMed]

104. Rocznik-Ferguson, A.; Petit, C.S.; Froehlich, F.; Qian, S.; Ky, J.; Angarola, B.; Walthier, T.C.; Ferguson, S.M. The transcription factor TFE3 links mTORC1 signaling to transcriptional control of lysosome homeostasis. Sci. Signal. 2012, 5, ra42. [CrossRef] [PubMed]

105. Medina, D.L.; Di Paola, S.; Peluso, I.; Armani, A.; De Stefani, D.; Venditti, R.; Montefusco, S.; Scotto-Rosato, A.; Prezioso, C.; Forrester, A.; et al. Lysosomal calcium signalling regulates autophagy through calcineurin and TFE3. Nat. Cell Biol. 2015, 17, 288–299. [CrossRef] [PubMed]

106. Bronisz, A.; Sharma, S.M.; Hu, R.; Godlewska, J.; Tzivion, G.; Mansky, K.C.; Ostrowski, M.C. Microphthalmia-associated transcription factor interactions with 14-3-3 modulate differentiation of committed myeloid precursors. Mol. Biol. Cell 2006, 17, 3897–3906. [CrossRef]

107. Napolitano, G.; Di Malta, C.; Esposito, A.; de Araujo, M.E.G.; Pece, S.; Beraldo, G.; Maset, F.; Benedetti, V.; Zampelli, A.; Stasyk, T.; et al. A substrate-specific mTORC1 pathway underlies Birt-Hogg-Dube syndrome. Nature 2020, 585, 597–602. [CrossRef]

108. Zhang, Z.; Qian, Q.; Li, M.; Shao, F.; Ding, W.X.; Lira, V.A.; Chen, S.X.; Sebag, S.C.; Hotamisligil, G.S.; Cao, H.; et al. The nuclear transport of TFEB. EMBO J. 2012, 31, 464–472. [CrossRef] [PubMed]

109. Miller, A.J.; Levy, C.; Davis, I.J.; Razin, E.; Fisher, D.E. Sumoylation of MITF and its related family members TFE3 and TFEB. J. Biol. Chem. 2006, 281, 24270–24277. [CrossRef] [PubMed]

110. Bronisz, A.; Sharma, S.M.; Hu, R.; Godlewska, J.; Tzivion, G.; Mansky, K.C.; Ostrowski, M.C. Microphthalmia-associated transcription factor interactions with 14-3-3 modulate differentiation of committed myeloid precursors. Mol. Biol. Cell 2006, 17, 3897–3906. [CrossRef]

111. Napolitano, G.; Espositio, A.; Choi, H.; Matarese, M.; Benedetti, V.; Di Malta, C.; Montefolregola, J.; Medina, D.L.; Lippincott-Schwartz, J.; Ballabio, A. mTOR-dependent phosphorylation controls TFE3 nuclear export. Nat. Commun. 2018, 9, 3312. [CrossRef] [PubMed]

112. Li, Y.; Xu, M.; Ding, X.; Yan, C.; Song, Z.; Chen, L.; Huang, X.; Wang, X.; Jian, Y.; Tang, G.; et al. Protein kinase C controls lysosome biogenesis independently of mTORC1. Nat. Cell Biol. 2016, 18, 1065–1077. [CrossRef] [PubMed]

113. Palmieri, M.; Pal, R.; Nelvagal, H.R.; Lotfi, P.; Stinnett, G.R.; Seymour, M.L.; Chaudhury, A.; Bajaj, L.; Bondar, V.V.; Bremner, L.; et al. mTORC1-independent TFE3 activation via Akt inhibition promotes cellular clearance in neurodegenerative storage diseases. Nat. Commun. 2017, 8, 14338. [CrossRef] [PubMed]

114. Wang, Y.; Huang, Y.; Liu, J.; Zhang, J.; Xu, M.; You, Z.; Peng, C.; Gong, Z.; Liu, W. Acetyltransferase GCN5 regulates autophagy and lysosome biogenesis by targeting TFE3. EMBO Rep. 2020, 21, e48335. [CrossRef]

115. Miller, A.J.; Levy, C.; Davis, I.J.; Razin, E.; Fisher, D.E. Sumoylation of MITF and its related family members TFE3 and TFEB. J. Biol. Chem. 2006, 281, 24270–24277. [CrossRef] [PubMed]

116. Martina, J.A.; Chu, S.; Jain, J.; de Ronza, A.; Pelz, C.; Sardiello, M.; Ballabio, A. Characterization of the CLEAR network reveals an integrated control of cellular clearance pathways. Hum. Mol. Genet. 2011, 20, 3852–3866. [CrossRef] [PubMed]

117. Chauhan, S.; Kumar, S.; Jain, A.; Ponpuak, M.; Mudd, M.H.; Huynh, T.; Ferron, M.; Karsenty, G.; Vellard, M.C.; Facchinetti, V.; et al. The unfolded protein response regulates hepatic autophagy by sXBP1-mediated activation of TFE3. Autophagy 2017, 13, 1841–1855. [CrossRef] [PubMed]

118. Yaffe, M.B.; Rittinger, K.; Volinia, S.; Caron, P.R.; Aitken, A.; Leffers, H.; Gamblon, S.J.; Smerdon, S.J.; Cantley, L.C. The structural basis for 14-3-3:phosphopeptide binding specificity. Cell 1997, 91, 961–971. [CrossRef]

119. Palmieri, M.; Impey, S.; Kang, H.J.; di Ronza, A.; Pelz, C.; Sardiello, M.; Ballabio, A. The complex relationship between TFE3 transcription factor phosphorylation and subcellular localization. EMBO J. 2018, 37, e98804. [CrossRef] [PubMed]

120. Napolitano, G.; Espositio, A.; Choi, H.; Matarese, M.; Benedetti, V.; Di Malta, C.; Montefolregola, J.; Medina, D.L.; Lippincott-Schwartz, J.; Ballabio, A. mTOR-dependent phosphorylation controls TFE3 nuclear export. Nat. Commun. 2018, 9, 3312. [CrossRef] [PubMed]

121. Li, Y.; Xu, M.; Ding, X.; Yan, C.; Song, Z.; Chen, L.; Huang, X.; Wang, X.; Jian, Y.; Tang, G.; et al. Protein kinase C controls lysosome biogenesis independently of mTORC1. Nat. Cell Biol. 2016, 18, 1065–1077. [CrossRef] [PubMed]

122. Decressac, M.; Mattson, B.; Weikop, P.; Lundblad, M.; Jakobsson, J.; Bjorklund, A. TFEB-mediated autophagy rescues midbrain dopamine neurons from alpha-synuclein toxicity. Proc. Natl. Acad. Sci. USA 2013, 110, E18171826. [CrossRef] [PubMed]

123. Brady, O.A.; Martina, J.A.; Puertollano, R. Emerging roles for TFE3 in the immune response and inflammation. Autophagy 2018, 14, 181–189. [CrossRef] [PubMed]

124. El-Houjeiri, L.; Possik, E.; Vijayaraghavan, T.; Paquette, M.; Martina, J.A.; Kazan, J.M.; Ma, E.H.; Jones, R.; Blanchette, P.; Puertollano, R.; et al. The transcription factors TFE3 and TFEB link the FLCN-AMPK Signaling Axis to Innate Immune Response and Pathogen Resistance. Cell Rep. 2019, 26, 3613–3628.e3616. [CrossRef] [PubMed]

125. Pastore, N.; Brady, O.A.; Diab, H.I.; Martina, J.A.; Sun, L.; Huynh, T.; Lim, J.A.; Zare, H.; Raben, N.; Ballabio, A.; et al. TFE3 cooperates in the regulation of the innate immune response in activated macrophages. Autophagy 2016, 12, 1240–1258. [CrossRef] [PubMed]

126. Martina, J.A.; Chen, Y.; Gucek, M.; Puertollano, R. MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFE3. Autophagy 2012, 8, 903–914. [CrossRef] [PubMed]
127. Campbell, G.R.; Rawat, P.; Bruckman, R.S.; Spector, S.A. Human Immunodeficiency Virus Type 1 Nef Inhibits Autophagy through Transcription Factor EB Sequestration. *PLoS Pathog.* 2015, 11, e1005018. [CrossRef] [PubMed]

128. Singh, N.; Kansal, P.; Ahmad, Z.; Baid, N.; Kushwaha, H.; Khatri, N.; Kumar, A. Antimycobacterial effect of IFNG (interferon gamma)-induced autophagy depends on HMOX1 (HEME oxygenase 1)-mediated increase in intracellular calcium levels and modulation of PPP3/calcineurin-TFEB (transcription factor EB) axis. *Autophagy* 2018, 14, 972–991. [CrossRef]

129. Visvikis, O.; Bluegebu, N.; Labed, S.A.; Luhachack, L.G.; Alves, A.F.; Wollenberg, A.C.; Stuart, L.M.; Stormo, G.D.; Irazoqui, J.E. Innate host defense requires transcriptional TFEB-mediated cytoprotective and antimicrobial genes. *Immunity* 2014, 40, 896–909. [CrossRef]

130. Gray, M.A.; Choy, C.H.; Dayam, R.M.; Ospina-Escobar, E.; Somerville, A.; Xiao, X.; Ferguson, S.M.; Botelho, R.J. Phagocytosis Enhances Lysosomal and Bactericidal Properties by Activating the Transcription Factor TFEB. *Curr. Biol.* 2016, 26, 1955–1964. [CrossRef]

131. Cinque, L.; De Leonibus, C.; Iavazzo, M.; Krahmer, N.; Intartaglia, D.; Salierno, F.G.; De Cegli, R.; Di Malta, C.; Svelto, M.; Lanzara, C.; et al. MIT/TFE factors control ER-phagy via transcriptional regulation of FAM134B. *EMBO J.* 2020, e105696. [CrossRef]

132. Kumar, S.; Jain, A.; Choi, S.W.; da Silva, G.P.D.; Allers, L.; Mudd, M.H.; Peters, R.S.; Anonsen, J.H.; Rusten, T.E.; Lazarou, M.; et al. Mammalian Atg8 proteins and the autophagy factor IRGCM control mTOR and TFEB at a regulatory node critical for responses to pathogens. *Nat. Cell Biol.* 2020, 22, 973–985. [CrossRef]

133. Weidberg, H.; Shvils, E.; Shpilka, T.; Shimron, E.; Shinder, V.; Elazar, Z. LC3 and GATE-16/GABARAP subfamilies are both essential yet act differently in autophagosome biogenesis. *EMBO J.* 2010, 29, 1792–1802. [CrossRef]

134. Weidberg, H.; Shpilka, T.; Shvils, E.; Abada, A.; Shimron, E.; Elazar, Z. LC3 and GATE-16 N termini mediate membrane fusion processes required for autophagosome biogenesis. *Dev. Cell* 2011, 20, 444–454. [CrossRef]

135. Nguyen, T.N.; Padman, B.S.; Usher, J.; Oorschot, V.; Ramn, G.; Lazarou, M. Atg8 family LC3/GABARAP proteins are crucial for autophagosome-lysosome fusion but not autophagosome formation during PINK1/Parkin mitophagy and starvation. *J. Cell Biol.* 2016, 215, 875–874. [CrossRef]

136. Gu, Y.; Princely Abudu, Y.; Kumar, S.; Bissa, B.; Choi, S.W.; Jia, I.; Lazarou, M.; Eskelinen, E.L.; Johansen, T.; Deretic, V. Mammalian Atg8 proteins regulate lysosome and autolysosome biogenesis through SNAREs. *EMBO J.* 2019, 38, e101994. [CrossRef] [PubMed]

137. Chauhan, S.; Mandell, M.A.; Deretic, V. IRGM Governs the Core Autophagy Machinery to Conduct Antimicrobial Defense. *Mol. Cell. 2015, 58, 507–521. [CrossRef]

138. Singh, S.B.; Ornatowski, W.; Vergne, I.; Naylor, J.; Delgado, M.; Roberts, E.; Ponpuak, M.; Master, S.; Pilli, M.; White, E.; et al. Human IRGM regulates autophagy and cell-autonomous immunity functions through mitochondria. *Nat. Cell Biol.* 2010, 12, 1154–1168. [CrossRef]

139. Settembre, C.; Fraaldi, A.; Medina, D.L.; Ballabio, A. Signals from the lysosome: A control centre for cellular clearance and energy metabolism. *Nat. Rev. Mol. Cell Biol.* 2013, 14, 283–296. [CrossRef]

140. Nnah, I.C.; Wang, B.; Saqcena, C.; Weber, G.F.; Bonder, E.M.; Bagley, D.; De Cegli, R.; Napolitano, G.; Medina, D.L.; Ballabio, A.; et al. TFEB-driven endocytosis coordinates MTORC1 signaling and autophagy. *Autophagy* 2019, 15, 151–164. [CrossRef]

141. Pedersen, N.M.; Wenzel, E.M.; Wang, L.; Antoine, S.; Chavrier, P.; Stenmark, H.; Raiborg, C. Protrudin-mediated ER-endosome contact sites promote MT1-MMP exocytosis and cell invasion. *J. Cell Biol.* 2020, 219, e202003063. [CrossRef]

142. Raiborg, C.; Wenzel, E.M.; Stenmark, H. ER-endosome contact sites: Molecular compositions and functions. *EMBO J.* 2015, 34, 1848–1858. [CrossRef] [PubMed]

143. Gu, Y.; Princely Abudu, Y.; Kumar, S.; Bissa, B.; Choi, S.W.; Jia, I.; Lazarou, M.; Eskelinen, E.L.; Johansen, T.; Deretic, V. Mammalian Atg8 proteins regulate lysosome and autolysosome biogenesis through SNAREs. *EMBO J.* 2019, 38, e101994. [CrossRef] [PubMed]

144. Muller, F. The nature and mechanism of superoxide production by the electron transport chain: Its relevance to aging. *J. Am. Aging Assoc.* 2000, 23, 227–253. [CrossRef] [PubMed]

145. Han, D.; Williams, E.; Cadenas, E. Mitochondrial respiratory chain-dependent generation of superoxide anion and its release into the intermembrane space. *Biochem. J.* 2001, 353, 411–416. [CrossRef] [PubMed]

146. Vermeulen, R.; Schymanski, E.L.; Barabasi, A.L.; Miller, G.W. The exposome and health: Where chemistry meets biology. *Science* 2020, 367, 392–396. [CrossRef] [PubMed]

147. Gracia-Cazana, T.; Gonzalez, S.; Parrado, C.; Juarranz, A.; Gilaberte, Y. Influence of the Exposome on Skin Cancer. *Actas Dermosifiliogr.* (Engl. Ed.) 2020, 111, e202003063. [CrossRef]

148. Muller, F. The nature and mechanism of superoxide production by the electron transport chain: Its relevance to aging. *J. Am. Aging Assoc.* 2000, 23, 227–253. [CrossRef] [PubMed]

149. Han, D.; Williams, E.; Cadenas, E. Mitochondrial respiratory chain-dependent generation of superoxide anion and its release into the intermembrane space. *Biochem. J.* 2001, 353, 411–416. [CrossRef] [PubMed]

150. Vermeulen, R.; Schymanski, E.L.; Barabasi, A.L.; Miller, G.W. The exposome and health: Where chemistry meets biology. *Science* 2020, 367, 392–396. [CrossRef] [PubMed]

151. Gracia-Cazana, T.; Gonzalez, S.; Parrado, C.; Juarranz, A.; Gilaberte, Y. Influence of the Exposome on Skin Cancer. *Actas Dermosifiliogr.* (Engl. Ed.) 2020, 111, e202003063. [CrossRef]

152. Vermeulen, R.; Schymanski, E.L.; Barabasi, A.L.; Miller, G.W. The exposome and health: Where chemistry meets biology. *Science* 2020, 367, 392–396. [CrossRef] [PubMed]

153. Muller, F. The nature and mechanism of superoxide production by the electron transport chain: Its relevance to aging. *J. Am. Aging Assoc.* 2000, 23, 227–253. [CrossRef] [PubMed]

154. Han, D.; Williams, E.; Cadenas, E. Mitochondrial respiratory chain-dependent generation of superoxide anion and its release into the intermembrane space. *Biochem. J.* 2001, 353, 411–416. [CrossRef] [PubMed]

155. Vermeulen, R.; Schymanski, E.L.; Barabasi, A.L.; Miller, G.W. The exposome and health: Where chemistry meets biology. *Science* 2020, 367, 392–396. [CrossRef] [PubMed]
180. Kenific, C.M.; Thorburn, A.; Debnath, J. Autophagy and metastasis: Another double-edged sword. Curr. Opin. Cell Biol. 2010, 22, 241–245. [CrossRef] [PubMed]

181. Pavlova, N.N.; Thompson, C.B. The Emerging Hallmarks of Cancer Metabolism. Cell Metab. 2016, 23, 27–47. [CrossRef] [PubMed]

182. Mauthe, M.; Orhon, I.; Rocchi, C.; Zhou, X.; Luhr, M.; Hijlkema, K.J.; Engedal, N.; Mari, M.; Reggiori, F. Chloroquine inhibits autophagic flux by decreasing autophagosome–lysosome fusion. Autophagy 2018, 14, 1435–1455. [CrossRef] [PubMed]

183. DeBerardinis, R.J.; Chandel, N.S. Fundamentals of cancer metabolism. Sci. Adv. 2016, 2, e1600200. [CrossRef] [PubMed]

184. Nazio, F.; Bordi, M.; Cianfanelli, V.; Locatelli, F.; Ceconi, F. Autophagy and cancer stem cells: Molecular mechanisms and therapeutic applications. Cell Death Differ. 2019, 26, 690–702. [CrossRef]

185. Levy, J.M.; Thompson, J.C.; Griesinger, A.M.; Amani, V.; Donson, A.M.; Birks, D.K.; Morgan, M.J.; Mirsky, D.M.; Handler, M.H.; Foreman, N.K.; et al. Autophagy inhibition improves chemosensitivity in BRAF(V600E) brain tumors. Cancer Discov. 2014, 4, 773–780. [CrossRef]

186. Stransky, L.; Cotter, K.; Forgac, M. The Function of V-ATPases in Cancer. Physiol Rev. 2016, 96, 1071–1091. [CrossRef]

187. Wang, Q.; Yao, J.; Lin, Q.; Wang, X.; Zhu, H.; Huang, F.; Wang, W.; Qiang, J.; Ni, Q. LAMP1 expression is associated with poor prognosis in breast cancer. Oncol. Lett. 2018, 435, 32–43. [CrossRef]

188. Ronan, B.; Flamand, O.; Vescovi, L.; Dureuil, C.; Durand, L.; Fassy, F.; Bachelot, M.F.; Lamberton, A.; Mathieu, M.; Bertrand, T.; et al. A novel ATG4B antagonist inhibits autophagy and has a negative impact on osteosarcoma tumors. Autophagy 2014, 10, 1013–1019. [CrossRef]

189. Egan, D.F.; Chun, M.G.; Vamos, M.; Zou, H.; Rong, J.; Miller, C.J.; Lou, H.J.; Raveendra-Panickar, D.; Yang, C.C.; Sheffler, D.J.; et al. Small Molecule Inhibition of the Autophagy Kinase ULK1 and Identification of ULK1 Substrates. Mol. Cell 2015, 59, 285–297. [CrossRef]

190. Hamura, R.; Shirai, Y.; Shimada, Y.; Saito, N.; Taniai, T.; Horiuchi, T.; Takada, N.; Kanegae, Y.; Ikegami, T.; Ohashi, T.; et al. TFEB-GDF15 axis regulates autophagy in anoikis-resistant glioma stem cells. Proc. Natl. Acad. Sci. USA 2018, 115, 5768–5773. [CrossRef]

191. Talukdar, S.; Pradhan, A.K.; Bhooopathi, P.; Shen, X.N.; August, L.A.; Windle, J.J.; Sarkar, D.; Furnari, F.B.; Cavenee, W.K.; Das, S.K.; et al. MDA-9/Sytenerin regulates protective autophagy in anoikis-resistant glioma stem cells. Proc. Natl. Acad. Sci. USA 2016, 113, 20016–20021. [CrossRef]

192. White, E. The role for autophagy in cancer. J. Clin. Investig. 2015, 125, 42–46. [CrossRef]

193. Akin, D.; Wang, S.K.; Habibzadegah-Tari, P.; Law, B.; Ostrov, D.; Li, M.; Yin, X.M.; Kim, J.S.; Horenstein, N.; Dunn, W.A.; et al. Akin, D.; Habibzadegah-Tari, P.; Law, B.; Ostrov, D.; Li, M.; Yin, X.M.; Kim, J.S.; Horenstein, N.; Dunn, W.A., Jr. Autophagy links MYC signaling to epigenetic control of myeloid differentiation and acute myeloid leukemia. Blood Cancer Discov. 2014, 4, 377–388. [CrossRef] [PubMed]

194. Mauthe, M.; Orhon, I.; Rocchi, C.; Zhou, X.; Luhr, M.; Hijlkema, K.J.; Engedal, N.; Mari, M.; Reggiori, F. Chloroquine inhibits autophagic flux by decreasing autophagosome–lysosome fusion. Autophagy 2018, 14, 1435–1455. [CrossRef] [PubMed]

195. Kallunki, T.; Olsen, O.D.; Jaattela, M. Cancer-associated lysosomal changes: Friends or foes? J. Clin. Investig. 2021, 131, e146821. [CrossRef]

196. Rabinovich-Nikitin, I.; Kirshenbaum, L.A. YAP/TFEB pathway promotes autophagic cell death and hypertrophic cardiomyopathy in lysosomal storage diseases. J. Clin. Investig. 2021, 131, e146821. [CrossRef]
207. Arguello, G.; Balboa, E.; Tapia, P.J.; Castro, J.; Yanez, M.J.; Mattar, P.; Pulgar, R.; Zanlungho, S. Genisten fibrosis Transcription Factor EB and Corrects Niemann-Pick C Phenotype. *Int. J. Mol. Sci.* 2021, 22, 4220. [CrossRef]

208. Gu, M.; Jin, J.; Ren, C.; Chen, X.; Pan, Z.; Wu, Y.; Tian, N.; Sun, L.; Wu, A.; Gao, W.; et al. 20-Deoxyxynol alleviates osteoarthritis by activating TFEB in chondrocytes. *Pharm. Res.* 2021, 28, 105361. [CrossRef]

209. Wu, C.; Chen, H.; Zhuang, R.; Zhang, H.; Wang, Y.; Hu, X.; Xu, Y.; Li, J.; Li, Y.; Wang, X.; et al. Betulinic acid inhibits pyroptosis in spinal cord injury by augmenting autophagy via the AMPK-mTOR-TFEB signaling pathway. *Int. J. Biol. Sci.* 2021, 17, 1138–1152. [CrossRef]

210. Wang, Z.; Yang, C.; Liu, J.; Chun-Kit Tong, B.; Zhu, Z.; Malampati, S.; Gopalkrishnaswthetty Sreenivasamurthy, S.; Cheung, K.H.; Iyawasmy, A.; Su, C.; et al. A Curcumin Derivative Activates TFEB and Protects Against Parkinsonian Neurotoxicity in Vitro. *Int. J. Mol. Sci.* 2020, 21, 1515. [CrossRef]

211. Faraghasse, Y.; Maios, C.; Parker, J.A. Small Molecule Rescue of ATXN3 Toxicity in *C. elegans* via TFEB/HLH-30. *Neurotherapeutics* 2021, 18, 1151–1165. [CrossRef]

212. Yang, Z.; Chee, C.E.; Huang, S.; Sincrope, F.A. The role of autophagy in cancer: Therapeutic implications. *Mol. Cancer* 2011, 10, 1533–1541. [CrossRef]

213. Motzer, R.J.; Escudier, B.; Oudard, S.; Hutson, T.E.; Porta, C.; Bracarda, S.; Grunwald, V.; Thompson, J.A.; Figlin, R.A.; Hollaender, N.; et al. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008, 372, 449–456. [CrossRef]

214. Ganipineni, L.P.; Danhier, F.; Preat, V. Drug delivery challenges and future of chemotherapeutic nanomedicine for glioblastoma treatment. *J. Control. Release* 2018, 281, 42–57. [CrossRef] [PubMed]

215. Guerrini, L.; Alvarez-Puebla, R.A.; Pazos-Perez, N. Surface Modifications of Nanoparticles for Stability in Biological Fluids. *Materials* 2018, 11, 1154. [CrossRef] [PubMed]

216. Pagliari, F.; Mandoli, C.; Forte, G.; Magnani, E.; Pagliari, S.; Nardone, G.; Licoccia, S.; Minieri, M.; Di Nardo, P.; Traversa, E. Cerium oxide nanoparticles protect cardiac progenitor cells from oxidative stress. *ACS Nano* 2012, 6, 3767–3775. [CrossRef]

217. Williams, K.A.; Veenhuizen, PT; de la Torre, B.G.; Eritja, R.; Dekker, C. Nanotechnology: Carbon nanotubes with DNA recognition. *Nature* 2002, 420, 761. [CrossRef] [PubMed]

218. Shi, Y.; van der Meel, R.; Chen, X.; Lammers, T. The EPR effect and beyond: Strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. *Theranostics* 2020, 10, 7921–7924. [CrossRef]

219. Lafuente-Gomez, N.; Milan-Rois, P.; Garcia-Soriano, D.; Luengo, Y.; Cordani, M.; Alarcon-Iniesta, H.; Salas, G.; Somoza, A. Smart *Combination*

220. Gonzalez-Pastor, R.; Lancelot, A.; Morcuende-Ventura, V.; San Anselmo, M.; Sierra, T.; Serrano, J.L.; Martin-Duque, P. *Modification on Magnetic Nanoparticles Dramatically Enhances Their Therapeutic Properties. Cancers* 2021, 13, 4095. [CrossRef]

221. Kubota, T.; Kuroda, S.; Kanaya, N.; Morihiro, T.; Aoyama, K.; Kakiuchi, Y.; Kikuchi, S.; Nishizaki, M.; Kagawa, S.; Tazawa, H.; et al. Autophagy inhibitor Lys05 has single-agent antitumor activity and reproduces the phenotype of a genetic autophagy deficiency. *Proc. Natl. Acad. Sci. USA* 2012, 109, 8253–8258. [CrossRef]

222. Ma, Z.; Li, J.; Lin, K.; Ramachandran, M.; Zhang, D.; Showalter, M.; De Souza, C.; Lindstrom, A.; Solano, L.N.; Jia, B.; et al. Autophagy inhibitor Lys05 has single-agent antitumor activity and reproduces the phenotype of a genetic autophagy deficiency. *Proc. Natl. Acad. Sci. USA* 2012, 109, 8253–8258. [CrossRef]

223. McAfee, Q.; Zhang, Z.; Samanta, A.; Levi, S.M.; Ma, X.H.; Piao, S.; Lynch, J.P.; Uehara, T.; Sepulveda, A.R.; Davis, L.E.; et al. Autophagy and chirality dependent autophagy effects. *J. Mater. Chem. B*

224. Bhowmik, T.; Gomes, A. NKCT1 (purified Naja kaouthia protein toxin) conjugated gold nanoparticles induced Akt/mTOR and activate the lysosome-autophagy system and enhance autophagic clearance. *Nat. Commun.* 2020, 11, 4615. [CrossRef]

225. Kubota, T.; Kuroda, S.; Kanaya, N.; Morihiro, T.; Aoyama, K.; Kakiuchi, Y.; Kikuchi, S.; Nishizaki, M.; Kagawa, S.; Tazawa, H.; et al. HER2-targeted gold nanoparticles potentially overcome resistance to trastuzumab in gastric cancer. *Nanomedicine* 2018, 14, 1919–1929. [PubMed]

226. Bhowmik, T.; Gomes, A. NKCT1 (purified Naja kaouthia protein toxin) conjugated gold nanoparticles induced Akt/mTOR inactivation mediated autophagic and caspase 3 activated apoptotic cell death in leukemic cell. *Toxicon* 2016, 121, 86–97. [CrossRef]

227. Rauf, A.; Imran, M.; Khan, I.A.; Ur-Rehman, M.; Gilani, S.A.; Mehmood, Z.; Mubarak, M.S. Anticancer potential of quercetin: A comprehensive review. *Phytother. Res.* 2018, 32, 2109–2130. [CrossRef] [PubMed]

228. Cordani, M.; Somoza, A. Targeting autophagy using metallic nanoparticles: A promising strategy for cancer treatment. *Cell Mol. Life Sci.* 2019, 76, 1215–1242. [CrossRef] [PubMed]

229. Khan, M.I.; Mohammad, A.; Patil, G.; Naqvi, S.A.; Chauhan, L.K.; Ahmad, I. Induction of ROS, mitochondrial damage and autophagy in lung epithelial cancer cells by iron oxide nanoparticles. *Biomaterials* 2012, 33, 1477–1488. [CrossRef]

230. Peng, Z.; Yuan, L.; XuHong, J.; Tian, H.; Zhang, Y.; Deng, J.; Qi, X. Chiral nanomaterials for tumor therapy: Autophagy, apoptosis, and photothermal ablation. *J. Nanobiotechnol.* 2019, 17, 220. [CrossRef]

231. Yuan, L.; Zhang, F.; Qi, X.; Yang, Y.; Yan, C.; Jiang, J.; Deng, J. Chiral polymer modified nanoparticles selectively induce autophagy of cancer cells for tumor ablation. *J. Nanobiotechnol.* 2018, 16, 55. [CrossRef]

232. Wang, Y.; Xia, Y. Near-infrared optically active Cu2–S nanocrystals: Sacrificial template-ligand exchange integration fabrication and chirality dependent autophagy effects. *J. Mater. Chem. B* 2020, 8, 7921–7930. [CrossRef]

233. Song, W.; Soo Lee, S.; Savini, M.; Popp, L.; Colvin, V.L.; Segatori, L. Ceria nanoparticles stabilized by organic surface coatings activate the lysosome-autophagy system and enhance autophagic clearance. *ACS Nano* 2014, 8, 10328–10342. [CrossRef]
232. Wei, P.F.; Zhang, L.; Nethi, S.K.; Barui, A.K.; Lin, J.; Zhou, W.; Shen, Y.; Man, N.; Zhang, Y.J.; Xu, J.; et al. Accelerating the clearance of mutant huntingtin protein aggregates through autophagy induction by europium hydroxide nanorods. *Biomaterials* **2014**, *35*, 899–907. [CrossRef] [PubMed]

233. Peynshaert, K.; Manshian, B.B.; Joris, F.; Braeckmans, K.; De Smedt, S.C.; Demeester, J.; Soenen, S.J. Exploiting intrinsic nanoparticle toxicity: The pros and cons of nanoparticle-induced autophagy in biomedical research. *Chem. Rev.* **2014**, *114*, 7581–7609. [CrossRef] [PubMed]

234. Romero, E.L.; Morilla, M.J. Preclinical autophagy modulatory nanomedicines: Big challenges, slow advances. *Expert Opin. Drug Deliv.* **2021**, *18*, 1–19. [CrossRef] [PubMed]