RECENT ADVANCES IN CANCER TREATMENT TARGETING AUTOPHAGY AND FUTURE ASPECTS

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

This study does not involve any human and animal trial.

Abstract/ Executive Summary

Lysosomal autophagy controls cellular homeostasis by degrading and recycling cytoplasmic molecules and organelles in the lysosome. This process in neuronal cells protects cognitive decline by removing abnormal intracellular protein accumulation. Since autophagy is well-known, new regulators of the process are expected to be discovered. It has been hypothesized that modulating autophagy can be employed as a therapeutic mechanism to boost the efficacy of traditional medicines, such as chemotherapy and radiation therapy. Thus, a critical concern in cancer therapy is whether to promote or inhibit autophagy. To enable the successful development of treatments targeting autophagy, a complete knowledge of the molecular components of autophagy is addressed here, with a particular emphasis on druggable targets, combination therapy are also explored as well as the possible hurdles and constraints for the application of these innovative therapeutic techniques in clinical practice.

Keyword: autophagy, autophagic cell death, anticancer therapy, chemotherapy, autophagy inhibitors

Dedication

Dedicated to my parents

Acknowledgement

First and foremost, I would like to express my gratitude to the Almighty for his endless gifts, which have been given to me in an effort to provide me with the strength and determination to complete this project.

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List of Acronyms

ACD	autophagic cell death
AMPK	AMP-activated protein kinase
ATG	Autophagy-related proteins
ATG16L1	Autophagy-related 16-like protein 1
BafA	BafilomycinA
BH3	Bcl-2 Homology 3
BRAF	v-Raf murine sarcoma viral oncogene homolog B
CMA	Chaperone Mediated Autophagy
CB1 y 2	Cannabinoid receptor 1 y 2
CCI779	Cell Cycle Inhibitor 779
CML	Chronic Myeloid Leukemia
CQ	Chloroquine
CSC	Cancer stem cell
DCMI	Desmethylclomipramine
DQ	Dimeric quinacrine
EGFR	Epidermal growth factor receptors
ER	Endoplasmic reticulum
HCQ	Hydroxychloroquine
HDAC	Histone deacetylase
HDACIs	Histone deacetylase inhibitors
LAMP2	Lysosome-associated membrane protein 2
LC3	Microtubule-associated protein light chain 3
MQ	Mefloquine
mTORC1	Mammalian target of rapamycin complex 1

mTORC2	Mammalian target of rapamycin complex 2
PE	Phosphatidylethanolamine
PI3K	Phosphoinositide 3-kinase
PI3KC1	The class I phosphatidylinositol 3-kinase
PI3KC3	The class III phosphatidylinositol 3-kinase
STX17	Syntaxin 17
THC	Tetrahydrocannabinol
TK	Tyrosin Kinase
TOR	Target of rapamycin
TRB3	Telomer repeat binding factor 3
ULK	(Unc)-51–Like Kinase proteins
VPS15	Vacuolar Protein Sorting 15
VPS34	Vacuolar Protein Sorting 3

Chapter 01

Introduction

Cancer has become a serious public health hazard in recent decades as a result of its high incidence and fatality rates. Human malignancies have been treated using a variety of treatments, including chemotherapy, surgery, targeted therapy, radiation and a combination of all these therapies. (Lei et al. 2017a). Autophagy is a significant catabolic mechanism that regulates cellular homeostasis through the degradation and recycling of cytoplasmic chemicals and organelles in lysosomes.

1.1. Cancer and Autophagy

Cancer is a condition in which some cells in the body grow out of control and spread to other areas of the body. Cancer can begin practically anywhere in the billions of cells that comprise the human body. Human cells normally expand and multiply (a process called cell division) to generate new cells as the body requires them. When cells get old or damaged, they die and are replaced by new cells. Using autophagy the body's cells get rid of anything that isn't needed or is damaged. There are three main types of autophagy: Chaperone-mediated autophagy (CMA), Microautophagy and Macroautophagy. They are all based on how intracellular components are sent to the lysosome for destruction. Several cellular activities, including development, differentiation, response to nutritional deficiency and oxidative stress, cell death, and the turnover of macromolecules and organelles, are controlled by the autophagic process. This is linked to cancer because of its pro-survival and pro-death properties. Its pro-survival activity aids cancer cells in surviving in nutrient-depleted environments. Conversely, the pro-death effect aids in the demise of cancer cells, either naturally or in response to radiation and chemotherapy.

1.2. Aim of the project

Autophagy has recently been recognized as a potential treatment in a variety of disorders other than cancer. Here, we will focus on cancer which is the most common cause of death in the world, responsible for over 10 million fatalities in 2020, or nearly one in every six deaths. To treat cancer patients many types of treatment are available but the result is not up to the mark. So researchers are continuously trying to bring new drugs or treatment strategies for different types of cancer. Targeting autophagy is one of them. Aim of the research is to technique development required for identifying new targets and inhibitors also analyzing clinical studies to improve the combination of drugs.

1.3. Objectives of this study

The objective of this study are-

- To know the process of targeting autophagy.
- To provide an insight into the treatment strategies using this.
- To make better decisions about modifying autophagy throughout cancer treatment.

Chapter 02

Methodology

This article provides a comprehensive summary of several cancer treatment options that target autophagy. Information for this review paper was gathered from peer-reviewed published studies, news items, academic published papers, and web sites. Furthermore, for this study, articles from prestigious journals such as Springer, Nature, Cells, The Lancet, MDPI, Frontiers, Bio pharma, Taylor and Francis were evaluated. Many articles were consulted for information and data, which aided in determining the importance and future of targeting autophagy. All of the information was collated and properly referenced, resulting in a greater understanding. Attempts were made to discover gaps or withholding data in the available literature.

However, approximately 120 clinical studies investigating the autophagic mechanism have been initiated thus far. (Chude and Amaravadi 2017; Mizushima 2007). The majority of this research focuses on autophagy in treating cancer and has earlier proven promising results, for example, when chloroquine or hydroxychloroquine is administered alone or in conjunction with other agents. Autophagy can be regulated by the development of autophagosomes surrounding protein aggregates or damaged organelles via the activities of autophagosomal membrane receptors. Through the removal of aberrant intracellular protein buildup, this mechanism in neuronal cells prevents cognitive decline

Autophagy has recently been recognized as a potential treatment in a variety of disorders other than cancer. (Towers and Thorburn 2010a). Numerous studies indicate that autophagy enhancers may inhibit the growth of cancer cells in premalignant lesions. (Galluzzi et al. 2015). In advanced malignancies, however, both increasing and suppressing autophagy have been proposed as treatment methods. (Levy and Thorburn 2011; Towers and Thorburn 2016)

Chapter 03

Pathway of Autophagy

Understanding autophagy, a multistep process, is crucial to generating strong tool substances and eventually, remedies that significantly modulate autophagy will be developed. Generally, autophagy pathway contains 7 steps, with autophagy genes which are conserved (ATG genes) regulate steps one to five, while genes Other endosomal/lysosomal routes get this feature stimulate processes six and seven. These seven steps are further divided into 4 sections. They are Initiation, Nucleation, Maturation and Degradation. (Ravikumar et al. 2010)

3.1. Initiation

Step 1: The Protein Kinase Complex of the Unc-51–Like Kinase Regulates the beginning of AV Formation. The complex of Unc-51-like kinase (ULK) contains a ULK family kinase, autophagy-related gene 13 (ATG13), and focal adhesion kinase interacting protein 200 kDa are all components of the ULK family of kinases (FIP200). Since mTORC1 is restricted or AMPK is activated, this complex becomes active. Hence, the ULK complex absorbs nutritional (mTOR) and AMPK (energy stress) signals from the cell's master controllers. Recent research shows that, to increase the connection of ATG13–FIP200 protein complex formation Tank Binding kinase 1 (TBK1 is needed. That helps the process by phosphorylating Syntaxin17. (Kumar et al. 2019)

3.2. Nucleation

Step 2: The VPS34 Lipid Kinase Complex curvatures the Membrane. In addition to activation of the Beclin1 (BECN1)-VPS34 complex, the complex also involves VPS15, Beclin1 regulator 1 (AMBRA-1) and ATG14L bdepending on the complex's subcellular location. (Behrends et

al. 2010) Step 2 is performed by the VPS34 lipid kinase complex.by generating membranes with phosphatidylinositol 3-phosphate (PI3P), usually from the endoplasmic reticulum (ER).

3.3. Maturation

Step 3: A protein from the LC3 family, cascade of LC3 Family Conjugation as an AV is conjugated to the membrane lipid, which helps identify it as such and allows it to receive cargo. This step involves WIPI2B binds to PI3P (Dooley et al. 2014), combining altogether two different protein conjugation mechanisms that are crucial for AV creation. When the WIP12B scaffold is available, ATG5 is converted to ATG12 by ATG7 and ATG10, which then creates a complex with ATG16L1. In AV membranes, the ATG5–ATG12–ATG6L1 the and ATG7–ATG3 complex are essential for LC3 (ATG8) family members (including GABARAPs) to be conjugated to the lipid phosphatidylethanolamine (PE) (Ravikumar et al. 2010; Walczak and Martens 2013). Meanwhile, the cysteine protease ATG4 is necessary to convert pro-LC3 to its soluble form before it can be conjugated to lipid by this cascade (LC3-I). When LC3 is conjugated to a lipid, it is placed onto the surface of the newly formed AV (Ichimura et al. 2000). On gel electrophoresis, the lipidated form of LC3 moves more quickly than the free form., hence the ratio of lipidated to free LC3 can be used to estimate the number of AVs growing at any specific time.

Step 4: LC3 conjugation on AVs serves as a flag for AVs as well as a docking site for autophagy cargo receptors that deliver autophagic cargo to AVs (see below). SQSTM1 (p62) and BRCA1's neighbor (NBR1) link to ubiquitinated proteins and organelles, allowing these to be autophagically degraded (Lamark et al. 2009). Cargo receptors enable selectivity in autophagy by binding specific cargo to specific cargo receptors (Gatica, Lahiri, and Klionsky 2018).

Step 5: Maturity of AV To seal the AV, ATG9 recruits lipid membrane from plasma membrane, mitochondria, Golgi, or endoplasmic reticulum to it (Orsi et al. 2012; Young et al. 2006). The separation membrane with trapped cargo is the AV. (Shibutani and Yoshimori 2014)

Step 6: The AV-Lysosome Fusion involves Rab GTPases, membrane-tethering complexes (HOPS complex, VPS genes), and soluble N-ethylmaleimide-sensitive factor attachment protein receptors (Nakamura and Yoshimori 2017).

3.4. Degradation

Step 7: AV Cargo Lysosomal Degradation Lysosomal enzymes degrade autophagic cargo, allowing recycled contents to escape, supporting cell development (Kimmelman and White 2017). Despite the fact that these 7 phases of autophagy are well-known, new autophagy regulators are likely to be uncovered. New autophagy regulators identified by siRNA screen in pancreatic cancer cell line. Cytosolic malate dehydrogenase 1 and MPP7 are attractive candidates for autophagosome formation (MDH1). MPP7 promotes YAP1, which causes autophagy, while MDH1 controls ULK1 levels. (New et al. 2019).

Chapter 04

Regulators of Autophagy In Cancer

Autophagy is triggered by metabolic or pharmacological stress through many molecular mechanisms. Here's a quick rundown of a few significant examples. There are also various other autophagy regulators that have been identified.

4.1. Direct Regulators

4.1.1. AMPK/Energy Stress

Energy stress in cancer cells can be induced by nutrition restriction or inhibitors of cancer cell metabolism, which act on the energy sensor 5′-AMP activated protein kinase 1 (AMPK1) and the nutrient sensor mTORC1. By inhibiting Raptor and Tuberous Sclerosis Complex 2 (TSC2), AMPK1 directly inhibits the mTORC1 regulators Raptor and TSC2 (Egan et al. 2011; Kim et al. 2011). This guarantees that autophagy is activated in a coordinated manner.

4.1.2. Growth Factor and Nutrient Stress Kinase Inhibitors

The collection of mTOR to the lysosome surface enhances mTOR activation via phosphorylation by the help of lysosome-bound RHEB. The lysosome which is being acidified by the vacuolar ATPase, acts as a scaffold for the RAG GTPase docking Regulator protein complex. The Raptor component of mTORC1 is recruited to lysosomes when amino acids are present (Bar-Peled et al. 2012; Sancak et al. 2010). RHEB completely activates mTORC1 once it reaches the lysosomal surface (Carroll et al. 2016). RHEB, the major activator of mTORC1, is inhibited by tuberous sclerosis complex 1 (TSC1/2). Growth factor (GF) transmission via the PI3K pathway regulates TSC2, which either activates or inhibits RHEB (Inoki et al. 2006).

Because RAG GTPases and RHEB reside in the lysosomes, the lysosomal surface is a crucial signaling pathway where global cellular health data is analyzed and transformed to mTORC1 activity condition Unlike AMPK-induced ULK1 phosphorylation, which leads to autophagy, mTORC1-induced ULK1 phosphorylation suppresses the VPS34 complex's downstream activity (Egan et al. 2011; Hosokawa et al. 1981). Inhibiting mTORC1 signaling by removing nutrients, using allosteric inhibitors (e.g. rapamycin derivatives), direct mTORC1 kinase inhibitors, AKT inhibitors, or PI3K inhibitors.

4.2. Autophagy Transcriptional Regulators Activated by Cancer Therapies

4.2.1. PI3K/mTOR Inhibitors and TFE Family

mTORC1 regulates autophagy transcriptionally and post-transcriptionally through changing the subcellular location of TFEB. Activated mTORC1 phosphorylates the TFEB/TFE3/MITF transcription factor family, which is then isolated in the cytoplasm. When the PI3K pathway or mTOR inhibitors inactivate mTORC1, TFE family members reach the nucleus and induce transcription of the CLEAR network of lysosome and autophagy genes. (Puertollano et al. 2018).

4.2.2. DNA-Damaging Agents and Activation of the p53 gene

The defender of the genome p53 induces autophagy by transcribing p53 targets (Kenzelmann Broz et al. 2013). The DNA damage response checkpoint proteins crucially regulate p53 directly and indirectly via mTORC1 and AMPK1 signaling.

4.2.3. BRD4 and Epigenetic Modulators

Recent research suggests that the chromatin reader protein BRD4 regulates lysosomal activity. (Sakamaki et al. 2017)The discovery of bromodomain inhibitors for cancer therapy makes this

important particularly for tumor therapy. Prosurvival autophagy is enhanced by the inhibition of BRD4, which may be useful in the clinic.

4.2.4. The ER Stress Response/Targeted Therapies

Previously, it has been demonstrated that ER stress induces autophagy. (Yorimitsu et al. 2006). For example, MYC expression triggers an ER stress response via PERK, which controls LC3 and promotes autophagic flux. ATG5 and ATG7 are preferentially translated due to PERK-dependent phosphorylation of eIF2 (Rzymski et al. 2010). 1α–dependent signaling, c-Jun N-terminal kinase (JNK) in inositol-dependent enzyme regulates autophagy via transcriptional activation, phosphorylation of B-cell lymphoma 2 (BCL2), and translocation of BECN1–BCL2 interaction.(Wei et al. 2008). ATF6 increases the production of death associated protein kinase 1, which directly regulates autophagy at various stages (Ojha et al. 2017). The ER stress response has recently been recognized as a link between mitogenic signaling and autophagy. Combining BRAF and MEK inhibition in BRAF-mutant melanoma, stimulates the conventional ER stress response, which induces autophagy. (Ma et al. 2014). In BRAF-mutant melanoma, the molecular mechanism of resistance linking MAPK pathway suppression to autophagy was recently described. MAPK inhibitors promote ER translocation via Sec61 translocase. Although the mechanism of ERK rephosphorylation remains unknown, it shows common resistance to MAPK inhibition. ER translocation is required for ERK reactivation. ERK reactivation also phosphorylates and stabilizes ATF4, which encodes many autophagy genes. To summarize, ER stress response programs link autophagy and ER reactivation to MAPK inhibitor resistance. (Ojha et al. 2019).

Chapter 05

Therapeutic Strategies

5.1. Stimulation of Autophagy in Cancer Treatment

ACD induction is an intriguing way to circumvent apoptosis resistance and leverage caspase independent cell death for cancer treatment. Compounds that work by inducing autophagy are detailed in the following sections.

Table 1: Compounds that operate by promoting autophagy

Mechanism of Action	**Name**
mTOR Inhibitors	Rapacmycin
	Temsirolimus (CCI779)
	Everolimus (RAD001)
	AZD8055
BH3 Mimetics	(-)-Gossypol(AT-101)
	Obatoclax (GX15-070)
	ABT-737

Cannabinoids	9-Tetrahydrocannabinol JWH-015
Histone Deacetylase Inhibitors	MHY2256
	Suberoylanilide hydroxamic acid (SAHA, Vorinostat)
Natural Products	Betulinic acid
	Curcumin
	Tocotrienol
	Resveratrol
Others	APO866
	Lapatinib

5.1.1. mTOR Inhibitors

mTOR regulates survival, cell growth, metabolism, and immunity. mTOR controls the cell cycle, autophagy and apoptosis. (Noda and Ohsumi 1998). Infection-fighting, anti-tumor, and immunosuppressive activities of rapamycin (sirolimus) from Streptomyces hygroscopicus (Sehgal, Baker, and Vézina 1975; Vézina and Kudelski 1975). Rapamycin and related rapalogs are allosteric selective mTORC1 inhibitors that alter downstream targets like autophagy activation (Benjamin et al. 2011; Pattingre et al. 2008). However, mTORC2 and other

compensatory signaling pathways are not blocked, the effectiveness of anti-tumor drugs is reduced. (Chiarini et al. 2019)

In mouse osteosarcoma, sarcoma (Shi et al. 2019), lung cancer, and neuroblastoma, rapamycin has been found to suppress proliferation and induce ACD. (Lin et al. 2018; Liu et al. 2013; Z. G. Xie, Xie, and Dong 2013) Temisirolimus (CCI779), on the other hand, has been shown to suppress tumor development in vitro in adenoid cystic carcinoma while also activating autophagy as a pro-survival strategy in renal-cell carcinoma (Liu et al. 2014; Singla and Bhattacharyya 2017). Furthermore, everolimus (or RAD001), the oral rapalog derivative induces cell cycle arrest in breast cancer cells via autophagy-mediated cyclin D1 degradation (Chen et al. 2019), but enhances autophagy in aromatase inhibitor-resistant breast cancer cells (Lui et al. 2016).

Other forms of mTOR inhibitors compete with ATP, preventing phosphorylation of its target proteins and thereby inhibiting mTOR more effectively. (Mao et al. 2017) AZD8055, for example, inhibits both mTOR complexes and has been demonstrated to reduce tumor development (Chresta et al. 2010) and induce ACD in hepatocellular carcinoma cell lines (Hu et al. 2014), but it can also inhibit the growth of tumor via inducing cell cycle arrest and apoptosis.(Chen et al. 2018) .These results suggest that mTOR stimulants may promote cell death in a tumor context-dependent way via multiple mechanisms, making them appropriate in order to tackle cancerous cells resistance by a combination therapy(Carew, Kelly, and Nawrocki 2011).

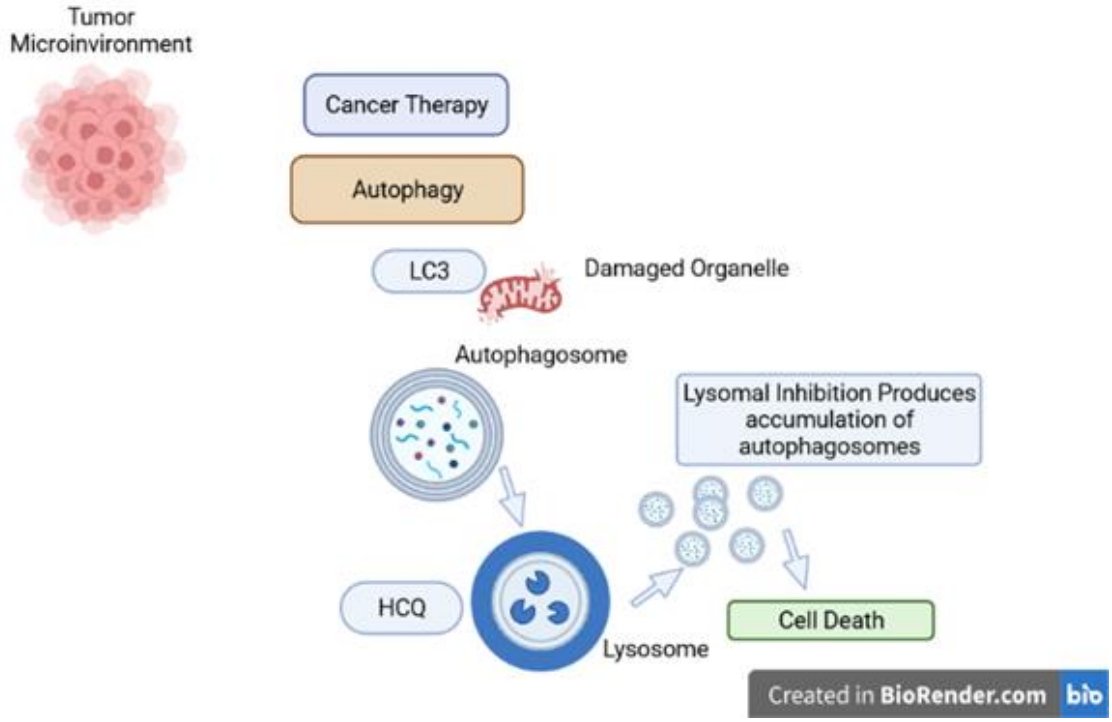

Figure 1: Targeting autophagy in cancer

5.1.2. BH3 Mimetics

BH3 (Bcl-2 homology 3) mimetics are a class of tiny compounds that replicate the BH3-only protein interactions.(Merino et al. 2018), which are a subset of the Bcl-2 family's pro-apoptotic proteins (Opydo-Chanek, Gonzalo, and Marzo 2017). BH3 mimetics, In general, by liberating Beclin-1 from Bcl-XL and Bcl2 inhibition, it may enhance autophagy (Koehler et al. 2015a; Opydo-Chanek et al. 2017). Gossypol is a cotton-derived BH3 mimic with strong affinity for Bcl-XL, Bcl-2, Bcl-w, and Mcl-1 (Opydo-Chanek et al. 2017). Its orally available enantiomeric form (-)-gossypol (AT-101) has been related to apoptosis in squamous cell carcinoma of the head and neck (Voss et al. 2010), colon cancer cells and malignant mesothelioma (Benvenuto et al. 2017, 2018; Lan et al. 2015). Another BH3 mimic, obatoclax (GX15-070), has demonstrated autophagic-mediated necroptosis in oral squamous cell cancer, acute

lymphoblastic leukemia cells and rhabdomyosarcoma cells (Basit, Cristofanon, and Fulda 2013; Bonapace et al. 2010; Sulkshane et al. 2016). Furthermore, without the participation of Beclin-1, obatoclax induced autophagy in adenoid cystic carcinoma (Liang et al. 2015) and inhibited autophagy in colorectal cancer cells. (Koehler et al. 2015b). Finally, ABT-737 was demonstrated to be efficient in vitro against hepatocellular carcinoma cells via autophagy mediated by Beclin-1. (Yao et al. 2017)

5.1.3 Cannabinoids

There are around 60 lipophilic cannabinoid ligands for distinct cell-surface cannabinoid receptors (CB1 and 2) present in the cannabis sativa plant, with THC being the most psychotropic (Śledziński et al. 2018). Cannabinoids has anticancer qualities due to their association with autophagy, however, depending on the cell type and cannabinoid used, they can also be cytoprotective (Costa et al. 2016). In melanoma cells, THC has been discovered to trigger non-canonical autophagy-mediated demise (Armstrong et al. 2015). and ACD present in glioma cells by autolysosome permeabilization, mTORC1 inhibition, apoptosis and cathepsin release. (Hernández-Tiedra et al. 2016; Salazar et al. 2009). JWH-015 is a CB2 receptor-selective synthetic cannabinoid agonist that was discovered to reduce tumor development in hepatocellular carcinoma cells via an autophagy-dependent mechanism and AMPK activation blocks the Akt/mTORC1 pathway in both in vitro and in vivo scenarios (Vara et al. 2011)

5.1.4. Histone Deacetylase Inhibitors (HDACIs)

The HDAC family have been investigated as anticancer agents due to their ability to influence gene expression (Newbold et al. 2016) which are consists of four classes (I-IV) of transcriptional repressors that affect chromatin structure (Mrakovcic, Kleinheinz, and Fröhlich

2017). Although it has been proposed that apoptosis occurs, as the primary mechanism for HDACI-induced cancer cell death, autophagy promotion has also been suggested, with the inactivation of PI3K/Akt/mTOR signaling being the most well-studied (Mrakovcic et al. 2018). For treating cutaneous T-cell lymphoma was suberoylanilide hydroxamic acid (SAHA, Vorinostat), a pan HDAC inhibitor, was the first HDACI approved by the FDA(Mann et al. 2007) and has been demonstrated to decrease tumor development in breast cancer cells in vitro via autophagy induction via Cathepsin B activation.(Han et al. 2017) Finally, Including both in vivo and in vitro research has established that MHY2256 causes death in endometrial cancer cells, ACD and cell cycle arrest. (De et al. 2018)

5.1.5. Natural Products

Based on autophagy stimulation, some natural substances have showed interesting anticancer properties. Betulinic acid is a triterpenoid with a pentacyclic structure tha found in a variety of plants that has been demonstrated to promote Multiple myeloma cells with high Bcl-2 expression have ACD. This derivative inhibits mitochondrial-mediated apoptosis while also increasing ACD by phosphorylating Beclin-1. (Zhou et al. 2017) Resveratrol, a polyphenol molecule found in plants, has been demonstrated to disrupt the Wnt/b-catenin signaling pathway, which inhibits cell growth in breast cancer stem-like cells.(Fu et al. 2014) Many malignancies have abnormally activated this system. Since it activates essential genes involved in tissue development and homeostasis, it has been linked to the autophagy process. Tocotrienol is one of four isomers of vitamin E that has been found to have lethal effects on prostate cancer cells in vitro by activating autophagy via ER stress.(Fontana et al. 2019) Curcumin, a significant component of Curcuma longa (turmeric), promotes autophagy, which has been demonstrated to have a dual effect in cell death and protection depending on the duration of therapy and concentration employed.(Deng et al. 2018)

5.2. Inhibition of Autophagy for the Treatment of Cancer

Some malignancies use autophagy to defend themselves, thus blocking it may help cure them. The table below lists various autophagy inhibitors that block autophagy at various stages

Table 2: Compounds that operate by inhibiting autophagy

Mechanism of Action	**Name**
ULK Inhibitors	Compound 6 MRT68921 MRT67307 SBI-0206965 ULK-100 ULK-101

Pan PI3k Inhibitors	3MA 3MA derivatives Wortmannin LY294002 SF1126 PI103 KU55933 Gö6976 GSK1059615
PI3KC3 Inhibitors	SAR405 Spautin-1 VPS34-IN1 Compound 31 PIK-III

ATG Inhibitors		LV320 S130 FMK-9a UAMC-2526 Tioconazol NSC185058 ATG7 inhibitor, miR154 ATG7 inhibitor
Autophagy Formation		Verteporfin
	Lysosomotropic Agents	Chloroquine Hydroxychloroquine Lys05 DQ661 VATG-027 Mefloquine Ganoderma lucidum polysaccharide (GLP)
	Vacuolar H+ ATPase Inhibitors	Bafilomycin A1

Lysosome Inhibitors	Ionophores	Tambjamines Monensin Squaramides
	Inhibition Autophagosome-Lysosome Fusion	Desmethylclomipramine Vacuolin-1 WX8 family
	Acid Protease Inhibitors	Pepstatin A E64d Leupeptin

5.2.1. ULK kinase Inhibitors

ULKs are a kind of protein kinase that forms complexes with other regulator units. Where ULK1 is needed for the initiation of autophagy, the involvement of ULK2 in autophagy seems to be dependent on cell type. (Lee et Tournier) The similarities of ULK1 and ULK2 inhibitors causes ULK1 to inhibit ULK2. (Chaikuad et al. 2019) ULK1 upregulation has been linked to poor susceptibility and treatment resistance in numerous malignancies. (Jiang et al. 2011; Yun et al. 2015; Zou et al. 2015). Inhibition of ULK1 reduces tumor development and induces apoptosis. (Dower et al. 2018; Tang et al. 2017). This led to the identification of inhibitors of kinase activity as compound 6, MRT67307, and MRT68921. (Lazarus, Novotny, and Shokat

2015; Petherick et al. 2015; Skah et al. 2018) Also, SBI-0206965 inhibits autophagy and increases apoptosis in the cell lines of neuroblastoma , NSCLC cells and clear cell renal cells of carcinoma. (Dower et al. 2018b; Egan et al. 2017b). It also inhibits AMPK, a kinase containing serine/threonine that triggers the ULK complex. (Dite et al. 2018) In recent years, further ULK inhibitors (ULK100 and ULk101) have been discovered, supporting the hypothesis that inhibiting ULK1 may be a suitable approach for cancer treatment.(Martin et al. 2018)

5.2.2. Inhibitors of Pan PI3K

The PI3K (The phosphoinositide 3-kinases') family is divided into three groups with differing substrate preferences. The role of Class II autophagy is still unknown. By the help of PI3K/Akt pathway, Class I activates mTORC1, while class III (VPS34) activates autophagy. (Lindmo and Stenmark, 2006) PI3K pathways are associated with cancer as it enhance proliferation of cell, migration, growth of blood vessels and survival.. So, these make better therapeutic targets .(Liu et al. 2009) Inhibiting autophagy is not the main impact of most PI3K inhibitors since they influence other cellular processes besides autophagy. Given their therapeutic value, we will quickly detail a few in the following.

3MA (3-Methyladenine), one of the earliest autophagy inhibitors, has two impacts on autophagy. (Seglen and Gordon 1982). It hinders autophagy by inhibiting PI3KC3 under starving conditions. In the presence of nutrients, it inhibits PI3KC1 and thus stimulates autophagy. (Wu et al. 2010). Moreover, reports say that it also lowers drug efflux transporter expression, bypassing taxol and doxorubicin resistance. (Zou et al. 2014)3MA works well at high doses but has solubility issues. Derivatives have been synthesized to address this constraint. (Wu et al. 2013) Wortmannin is a fungus metabolite that permanently binds PI3Ks in its site of catalytic action. (Thelen, Wymann, and Langen 1994). LY294002 is a poorly

soluble, short-half-life synthetic small molecule. Aggregating tissues of integrin-expression with SF1126 increases the solubility of LY294002 and drug kinetics, enhancing tumor site aggregation., and displaying anticancer and antiangiogenic activities in mice models. (Garlich et al. 2008) PI103, KU55933, Gö6976, and GSK1059615 are non-selective Pan PI3K inhibitors.(Farkas, Daugaard, and Jäättelä 2011; Ronan et al. 2014; Xie et al. 2017)

5.2.3. PI3KC3 Enzyme Containing VPS34 Complex Inhibitors

VPS34 transforms PI to PI3P. VPS34 is, in fact, a multi-subunit complex, including VPS15 (p150), ATG14, and Beclin-1, that are required for its activation. Inhibition of VPS34 activity can hinder autophagy. SAR405 is a (2S)-tetrahydropyrimido-pyrimidinone drug that hinders kinase activity via increased competition of ATP site. There are 200 protein kinases and 15 lipid kinases that favours PI3KC3 over the classes I and II. A lack of mTOR or starvation limits autophagy via SAR405. (Ronan et al. 2014). A bipyrimidinamine, VPS34-IN1 inhibits PI3KC3 out of over 300 tested protein kinases. (Bago et al. 2014) This hydrophobic pocket to which PIK-III, a bisaminopyrimidine, is bound is present only in VPS34 and is not seen in other VPS34-related kinases.(Dowdle et al. 2014) Compound 31 is a protein and lipid kinase inhibitor.(Pasquier et al. 2015) These four inhibitors target PI3KC3, although VPS34 can form complexes with other subunits, affecting its localization and activity alongside vesicle tracking. Such as SAR405, which inhibits both VPS34 complexes resulting an effect on endosomal tracking (Ronan et al. 2014). It may therefore influence cellular secretion. Spautin-1 indirectly reduces VPS34 activity by proteosomal decreasing of VPS34 complex forming proteins, deubiquitination of Beclin-1 is associated with both the USP10 and USP13.(Liu et al. 2011)

5.2.4. ATG inhibitors

VPS34 generating membrane PI3P binds ATG proteins and other components, aiding phagophore elongation. Inhibiting the development of the complexes inhibits autophagy. ATG7 is involved in ATG12-ATG5 complex formation and PE-LC3 and GABARAP conjugation. It has recently been discovered that ATG7 inhibitors (WO2018/089786), such as miR-154, can suppress the advancement of blade cancer that target ATG7 gene through micro RNAs (Zhang et al. 2019). To generate and detect autophagosomes, ATG4B cleaves LC3 and allows it to conjugate with PE. It is also essential for the recycling of LC3 and the fusion of autophagosome-lysosome. As a result, several ATG4B potential inhibitors have been evaluated in recent years as it can suppress autophagy more precisely. An osteosarcoma subcutaneous mouse model shows NSC185058 inhibits autophagy and autophagosome volume at the site of activation of ATG4B while suppressing tumor development. (Akin et al. 2014)Antifungal drug, tioconazole reduces cell viability and exposes the tumor cells to doxorubicin in a xenograft mouse model (Liu et al. 2018). There are also many ATG4B inhibitors that include a plasma-stable benzotropolone derivative, UAMC-2526 and a styrylquinoline, LV-320. These inhibits cell lines autophagy and cell proliferation in vivo. S130 and FMK-9a reduced LC3-PE delipidation but does not inhibit the formation of autophagosome. Some studies also look at indicators that can predict inhibitor efficacy.(Tran et al. 2013) For example, ATG4B inhibition only works in Her-2 positive cells.(Bortnik et al. 2016)

5.2.5. Inhibition of Autophagosome Formation

Verteporfin is a clinically utilized benzoporphyrin derivative. It suppresses autophagosome formation produced by depriving glucose and serum but does not inhibit mTOR inhibition (Donohue et al. 2011) Verteporfin may function by inhibiting p62 oligomerization, a protein needed for autophagosome sequestration of ubiquitinated targets. In addition to autophagy,

verteporfin suppresses Hippo pathway transcriptional co-activators, which has been linked to cell proliferation and stem cell activity. (Ota and Sasaki 2008) Verteporfin suppresses cell proliferation, motility, and angiogenesis while also inducing apoptosis. It suppresses autophagy in vivo but has no effect on tumor growth when used alone. It does, however, make tumor cells more sensitive to cytotoxic treatments. (Donohue et al. 2013)

5.2.6. Lysosome Inhibitors

Autophagosomes merge with lysosomes, destroying their contents. At this point, lysosomal inhibitors are used to block autophagy.

The drugs hydroxychloroquine (HCQ) and chloroquine (CQ) are used to treat malaria and, more recently, cancer. CQ/HCQ is a weak base that may cross cell membranes and infiltrate organelles like lysosomes, where high H+ concentrations promote protonation and elevate lysosomal pH. Protonated CQ/HCQ accumulates in lysosomes, increasing their bulk and decreasing enzyme activity. (Pérez-Hernández et al. 2019a)

Only CQ and HCQ are approved for clinical usage. Short-term treatment via CQ/HCQ therapy is considered safe, long-term HCQ medication has been linked to retinopathy in roughly 7.5 percent of patients as well as cardiac toxicity. The outbreak varies depending on the dosage regimen and treatment duration. This toxicity restriction, along with variations in clinical outcomes, has prompted the development of novel and more effective autophagy inhibitors (Bristol et al. 2013a). As a result of the development of CQ analogs with enhanced autophagy inhibition, Lys05 aggregates more readily in acidic organelles like lysosomes than that of HCQ. Lysosomal degradation and autophagy is inhibited by a dimeric quinacrine, DQ661, however, it also inhibits mTORC1 signaling by targeting palmitoyl-protein thioesterase-1. DQ661 has been proven to have effects in tumor animal models alone, and it has also overcome

gemcitabine resistance. (Rebecca et al. 2017)VATG-027 is another antimalaria drug that inhibits autophagy and has antitumoral effects. Mefloquine, on the other hand, accumulates in lysosomes, interrupting autophagy, inducing the apoptosis, and blocking MDR1, making it potent in tumor cells that are multidrug-resistant. Mefloquine creates sensitivity to chronic myeloid leukemia CML (Chronic Myeloid Leukemia) cells to TK inhibitors, favoring progenitor tumor cells over normal cells. (Lam Yi et al. 2019)

Ganoderma Lucidum Polysaccharide (GLP), is a polysaccharide having anticancer properties. CQ, along with its derivatives are not the only anti-autophagy drugs targeting lysosomes. GLP slows tumor development in mice and promotes cell death in cancer cells. (Wu et al. 2018) By lowering lysosome acidification, GLP reduces autophagy flux, which is thought to be the mechanism of inducing apoptosis. BafA (Bafilomycin A) blocks H+ entry into lysosomes, vacuoles and vesicles, preventing acidification. BafA also hinders autophagosome-lysosome fusion by altering the Ca2+ gradients associated.(Mauvezin and Neufeld 2015)

Ionophores can alter lysosomal pH and hence autophagy. The analogues of tambjamine, being ionophores that are anion selective, enhance mitochondrial expansion and prevent autophagy in cancer stem cells and lung cancer cells. The cation ionophores monensin, nigericin, and lasalocid are selective for lysosomes. Synthetic chloride transporters that also cause apoptosis.(Rodilla et al. 2017)

The WX8-family, on the other hand, consists of five chemical analogs that prevent lysosomes from fusing with autophagosomes, lysosomes from fissioning, and molecules from being sequestered in lysosomes keeping their pH unchanged. These compounds bind to PIKFYVE, a phosphoinositide kinase, and inhibit cancer growth in autophagic cells.(Sharma et al. 2019) However, Vacuolin-1 stimulates RAB5A, inhibiting both autophagosome-lysosome fusion and endosome-lysosome fusion, resulting in a deficiency of degrading endosome-lysosome.

Inhibition of autophagic flow and lysosomal breakdown by desmethylclomipramine (DCMI), which is a metabolite of Clomipramine (CM), an FDA-approved prodrug for mental diseases, makes the malignant cells more sensitive to the treatment of cancer cells. (Rossi et al. 2009). CSCs in the lungs are also affected by DCMI. Protease inhibitors like Pepstatin A (aspartyl proteases), E64D (cysteine proteases) and Leupeptin [155] can prevent lysosomal degradation. Nanoparticles, on the other hand, are commonly internalized by endocytosis, causing lysosome malfunction. (Stern, Adiseshaiah, and Crist 2012)

Chapter 06

CSCs And Autophagy in The Treatment of Anticancer

It's critical to look at the interaction between CSCs and autophagy because both play a vital role in resistance to anticancer therapy. Researchers discovered that the fusion of gemcitabine and autophagy inhibitors such as chloroquine made pancreatic CSCs more susceptible to gemcitabine. (Yang et al. 2015). Autophagy inhibition may interfere with the maintenance of CSCs. Because it could block autophagic flow, Wen Yue found salinomycin to be 100 times more productive than pacilitaxel at reducing breast CSCs. (Jiang et al. 2018). Researchers want to reduce the CD44+/CD24/low CSC population by deregulating DNA methyltransferase 1 (DNMT1) and Janus-activated kinase 2 (Jak2). Autophagy boosted PDT tolerance in CSCs, leading to colon cancer relapse and growth. (Wei et al. 2014). Autophagy can improve the efficacy of chemotherapy or any other anticancer therapies. It could be an aim for CSCs in terms of changing antitumor medication resistance. (Lei et al. 2017b)

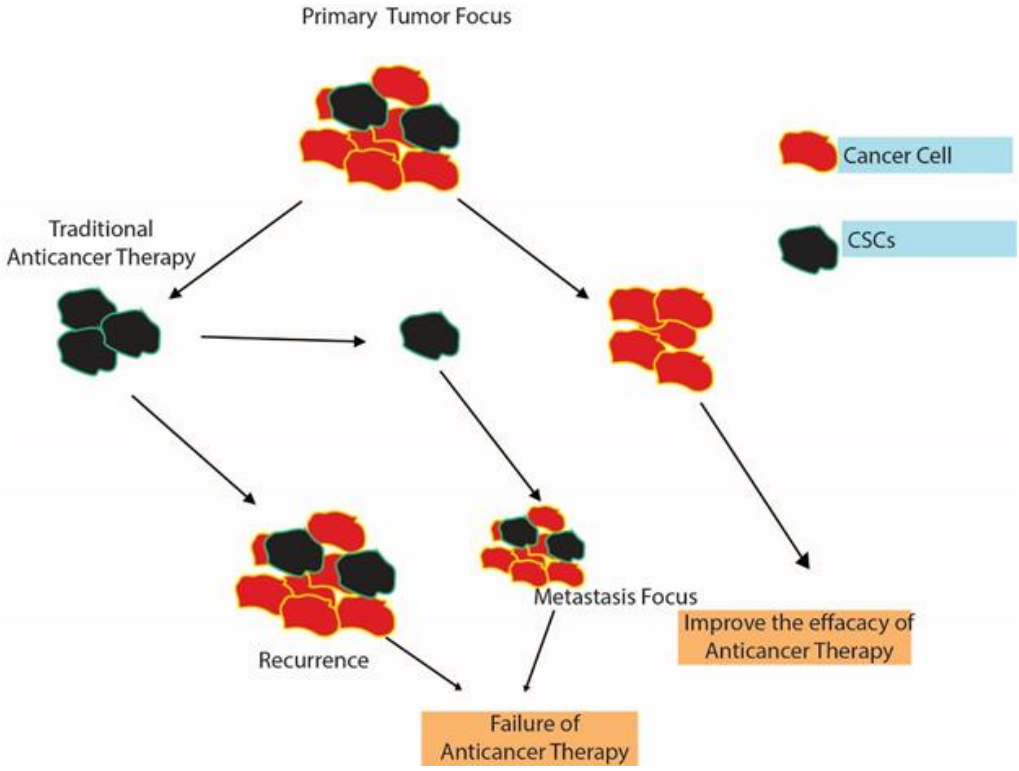

Figure 2: CSCs behaviors in cancer therapy

Chapter 07

Clinical Trials on Different Types of Cancers

Table 3: Ongoing Clinical Trials and Results

Compounds	**Treatment Strategies**	**Diseases**
Rapamycin	Autophagy induces targeting mTOR	MCF-7 Breast Cancer, B16 melanoma, Panic-1 pancreatic carcinoma
Metformin	Stimulates autophagy through AMPK activation	Prostate cancer cells, myeloma
Lithium Chloride	Induce inhibiting inositol mono phosphatase	Colorectal cancer
Bafilomycin A1	Promotes the binding of Beclin-1 to BCL-2, which inhibits autophagy	Gastric cancer cells
HCQ	Inhibit by suppressing the fusion process	B-cell chronic lymphocytic
HCQ + Temozolomide + Radiation	Inhibit by suppressing the fusion process combination help to kill more cell.	Glioblastoma multiforme

Chapter 08

Alternatives To Autophagy Inhibition

Since mTOR is an important negative regulatory axis for autophagy, several drugs that directly block it (temsirolimus, everolimus, rapamycin) have been used to activate it. By inhibiting signals essential for cell growth and proliferation, mTOR inhibition simulates cellular famine (Jung et al. 2010). Reports shown that the PI3K/AKT/mTOR system helps melanomas proliferate (Jung et al. 2010; X. Xie, White, and Mehnert 2013). The important autophagy gene (ATG7) is required for melanoma cell viability and its loss causes cell death. However, temsirolimus inhibiting mTOR promotes autophagy, which promotes tumor survival, limiting their efficacy. Combining HCQ with temsirolimus causes apoptosis in melanoma cells. Apoptic cell death followed by inhibition of melanoma development was induced by temsirolimus and HCQ in spheroid preparations and tumor xenografts. (X. Xie et al. 2013) According to these findings, inhibiting autophagy and mTOR pathways increases apoptosis and may introduce a different therapeutic approach for melanoma. Other techniques of triggering autophagy exist. In ER(–) and ER(+) orthotopic xenograft models and breast cancer cell lines, siRNA reduction of Bcl-2 expression causes autophagic cell death. (Akar et al. 2008; Tekedereli et al. 2013). PKC delta and TTG inhibition can increase apoptosis in pancreatic cancer cells. by inhibiting autophagy. Many cancer models have used JNK, MAPK, NF-kB, P38 or ERK (autophagy regulator) suppression or stimulation to alter autophagy responses to radiation therapy and chemo therapy. Therefore, studies show that there are diverse techniques for autophagy modulation that could improve therapy in some malignancies and that they could be used as co-therapy. (Ozpolat and Benbrook 2015)

Chapter 09

Discussion and Finding

Autophagy's two important concerns, that is, pro-survival or pro-death role in cancer is vital to determine, as in the stage of tumor growth at which autophagy should be addressed. Determining whether or not autophagy modulators are anti-apoptotic, pro-apoptotic, or protumorigenic will be critical in selecting them for cancer treatment. A gold standard biomarker, ideally derived from in-patient serum or plasma samples, will be a watershed moment in autophagy-cancer research, paving the way for more effective therapeutic interventions. Together, therapeutic manipulations of autophagy at various phases, via various receptors or signaling modulators, will be vital for the development of precision medicine for various cancer patients. (Ishaq et al. 2020). Oncogenic and non-oncogenic Ras-driven malignancies will be screened at large-scale for improved basal autophagy. These malignancies will expose a group of tumors that are selectively responsive to the autophagy suppression as a strategy to get optimum therapeutic effect. To attain this aim, technique development will be required due to the current methods' poor effectiveness in screening human tumor samples for basal autophagy. Autophagy inhibitor researchers face several challenges, including developing preclinical models, identifying new targets, and developing new inhibitors.In addition, clinical studies are now testing autophagy suppression as a monotherapy or in conjunction with chemotherapy or targeted treatment. (Mancias and Kimmelman 2011)

Chapter 10

Conclusion

Addressing autophagy for treating cancer appears to be a potential therapeutic technique, yet considerable hurdles have to be solved in order to enhance clinical results. Because the outcome of modifying autophagy is highly dependent on the tumor environment, it is critical to carefully establish which patients will benefit from which therapy before beginning any medical strategies.It's important to learn more about how autophagy influences cancer growth, find biomarkers that can help doctors figure out which patients will respond to a specific autophagy-mimicking drug, and find clear and better suited pharmacodynamic markers that can help doctors figure out how patients are responding. In addition, if we do better clinical studies and much more detailed cellular and molecular analysis to figure out why autophagy has different effects on cancer in different situations, we should be able to make better decisions about when and how to modify autophagy throughout cancer treatment. A better way to deal with this problem is to learn about how autophagy changes in cancer and afterwards apply this information in well-designed clinical trials, rather than just not dealing with the problem at all; this is what we should do instead.

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