Research Progress on the Mechanisms of Autophagy in Hepatocellular Carcinoma

Chizheng Zhu *

United World College of South East Asia (East Campus), Singapore

* Corresponding Author Email: zhu138672@gapps.uwcsea.edu.sg

Abstract. Autophagy, a cellular breakdown process, has two distinct roles in the progression of cancer: nutrition still furthers this; it is either a hindrance or propelling to tumor growth. Autophagy is the process of recycling cellular waste and is tightly controlled at the molecular level in hepatocellular carcinoma hepatocellular carcinoma (HCC). Through the process of consideration, the mechanisms (mTOR and AMPK pathways) along with the Beclin-1/Vps34 complex are distilled. The other main thing we touch on is how the cell sees the absence of a normal covert that leads to cancer cells. Due to the recent scientific and research milestones, autophagy has been proven to have its own genes and pathways, which form its characteristic in HCC. Thus, these discoveries have addressed areas leading to the identification of novel therapeutic targets therapeutically. Moreover, in this article, the clinical ramifications of autophagy in HCC are discussed. The implications of autophagy as a predictive factor, along with identified fetters and broadening frontiers in the employment of autophagy as a potential drug for the treatment of cancer, are involved. The purpose of the research is to pinpoint the complexity of autophagy in cancer treatment scope, as well as reveal unaddressed topics and focus the effort on the improvement of cancer treatments. This is accomplished by describing the current autophagy information related to HCC and the progress achieved in autophagy research regarding HCC. This review provided an overview of what was accomplished in the autophagy research process.

Keywords: Autophagy; Hepatocellular Carcinoma; Mechanism.

1. Introduction

Liver cancer in China: With 389,000 new cases per year, liver cancer is the fourth most common malignant tumor in China, with 336,000 deaths per year. Hepatocellular carcinoma (HCC) is the leading liver cancer type, which is the second most common cause of death from malignant tumors. Its incidence and mortality rates rising every passing year. Hepatocellular carcinoma has multiple causes, such as chronic hepatitis B and C infections, alcohol abuse, and non-alcoholic fatty liver disease. The difficulty of HCC consists not only in the multifactorial and diverse origin with chronic hepatitis B and C infections, alcohol abuse, and non-alcoholic fatty liver disease but also in the resistance to drug therapies, so it is urgent to find an effective anti-cancer measure now [1].

Autophagy puts forth that it is a bivalent function. Autophagy, triggered by lysosomes, cleans up the organelles, and the broken proteins help maintain many homeostatic processes. In the past, autophagy was mainly observed as a cell has a survival function. However, the investigation recently revealed further complexity, including autophagy as a tumor suppressor and promoter. These opposite roles have been affected by the tumor micro-environment stage of cancer development, which makes understanding the relation between autophagy and cancer much more complex. Hence, it is taken into account. The liver is unique in its metabolic demands and the role of autophagy in lipid and energy homeostasis. During HCC, the disordering of the autophagy route system may be involved in the initiation of cancer by meeting the metabolic needs of fast-dividing cancer cells, avoiding programmed cell death, and becoming tolerant to chemotherapy [2].

The review will provide a basis for a more extensive discussion of the autophagy pathway and its role in supporting the development of hepatic cell carcinoma, which would emphasize the promotional mechanism of the disease promotion and therapeutics. This paper will subsequently discuss the two major topics of HCC and autophagy, the molecular pathways of autophagy in HCC,

recent investigations, putative usages associated with the disease, and prospects of autophagy as an alternative approach in hepatocellular carcinoma treatment.

2. Introduction of Cellular Autophagy

Autophagy is a Greek word for self-eating. It is one of the crucial catabolic mechanisms involving the breakdown and recycling of cellular materials using lysosomal machinery. The overflow return line makes blood circulation incessant and performs a very important function, ensuring the discharge of non-functioning organelles, misfolded proteins, and foreign invaders. The cell, in turn, begins to withdraw from stressful situations. The significance of autophagy is that it plays a fundamental role in cell maintenance, but it also affects different physiological processes and diseases, such as cancer, neurodegeneration, and infection [3].

The beginning of self-devouring is the creation of a double-membrane vesicle. 'autophagosome' is the scientific name that is created to engulf cell materials that are intended for degradation. The autophagosome is next fused with a lysosome, which finally results in the formation of an autolysosome. The intracellular material is digested with the help of lysosomal enzymes that are present inside the lysosome. Then, the waste is brought back to the cytoplasm for further recycling. Herein, it is necessary to point out that the autophagic system is a sophisticated and precise process that is regulated by many autophagy-related (ATG) genes with their proteins involvement, which are vital for the initiation, nucleation, enlargement, and fusion of autophagosomes to lysosomes [4].

Using autophagy, the cell acts as a safeguard by getting rid of harmful materials before they accumulate and possibly damage the system. Under controlled environmental conditions, autophagy aids in executing functions designed for the daily upkeep of the cell and the organism's concentration levels. On the other hand, cell rates of autophagy may be greatly elevated so as to protect cellular integrity and even life in stressful conditions related to nutrient deprivation, low oxygen supply, or infection. This is done because the cell has to be ready to operate in unusual situations and keep active [5].

One of the most beneficial impacts of autophagy in the body is the maintenance of homeostasis. Still, the lack of regulation of autophagy is put forth as a cause for the manifestation of various disorders. Dysregulation of autophagy in cancer shows a complex and variable mode of action, exerting an anti-cancer effect in specific contexts and promoting cancer cell biology under other circumstances. Because autophagy carries both forceful and inhibiting functions towards the initiation and progression of cancer cells, it is suggested to be dual in nature, depending on the stage of cancer and its microenvironment surroundings [6].

Cellular autophagy activity is crucial in maintaining cells' health and keeping them balanced against environmental stressors. Its delicate management, aided by multiple roles in immunity and illness production, highlights the significance of analyzing mechanisms of autophagy, especially in cancer. The following paragraphs will discuss an exciting relationship between autophagy and hepatocellular carcinoma that may influence the formation or growth of cancer.

3. The Relationship between Cellular Autophagy and Hepatocellular Carcinoma

A relationship between autophagy and hepatocellular carcinoma functioning as a readiness for fight or flight is being thoroughly examined, with each one alternately contributing to cancer tumor development and causing it to regress. The encouragement of HCC by autophagy is not straightforward. Still, it suggests an intricate relation between cancer originating from the structure of cells during the fight for survival and then promoting it.

3.1. Promotion Effect on HCC

Autophagy aids in HCC development through several different methods. Another important aspect is the provision of energy and metabolic sources when there aren't enough of them due to microenvironmental stresses, such as hypoxic or nutrient scarcity, which happens to be found in tumors. This aid offers the cancer cells the opportunity to endure, propagate, and invade the new mature tissue in spite of unfavorable conditions. In addition, autophagia has a role in the self-cleaning of toxic debris, preventing the accumulation of these substances, which, otherwise, would act as their source. Such a feature better supports the implication of autophagy in live secretion with the liver, as the hepatic detoxification activity can cause the liver cells to be more exposed to damage and stress [7].

Direct molecular links are strongly involved in HCC autophagy promotion. The PI3K/Akt/mTOR pathway has a more predominant effect on this topic. It also plays a key role in regulating autophagy; therefore, it is frequently found to be dysregulated in cancers. In this situation, it is possible for the pathway to be inactivated with the subsequent autophagy suppression, leading to the uncontrolled growth of tumor cells. Hence, it provides the appropriate circumstance for cell growth and tumorous linear development. In other words, suppressing the mTOR pathway naturalizes autophagy, presenting a support factor to cancer cells coping with an unfriendly environment [6]. In addition, the p53 tumor suppressor gene also functions in another manner. Namely, this gene has the capability to induce autophagy in specific nutrient levels. Another study revealed that the p53 gene, for the most part, has an abnormalcy in about half of HCC cases. Such mutations could drastically alter the regular autophagic response to pressures and accelerate the damage of the tumor, so they are involved in the acquisition of malignant traits [8].

A number of biological mechanisms of autophagy as the pivotal HCC event were established and found to be significant prerequisites for HCC carcinogenesis. The sector consists of studying what exactly the miRNAs (microRNAs), through which the microcosm affects the progression of HCC, do when they target the MMA-related genes. Studies have shown that miR-106b is a constituent that has the ability to interact with DAB2, a pro-autophagy gene, leading to boosted hepatocellular carcinoma progression [9]. This ensures that the golden cross way of autophagy and the numerous setup circuits controlling cancer and their influence the latter.

Briefly, autophagy in the liver promotes liver cancer by means of various processes such as metabolic maintenance during stress, removal of injured cellular constituents, and regulatory functions of autophagic pathways and miRNAs. Hence, targeting the mitochondria and autophagy to build a novel therapeutic strategy becomes more crucial in hepatocellular cancer (HCC) treatment.

3.2. Inhibition Effect on HCC

Although autophagy may be a propeller promoter of HCC in specific scenarios, it also has the capability to hinder the growth and development of tumors. The ambiguity of autophagy is a relevant factor in cancer cell biology that makes the role of autophagy a difficult task to ascertain [10]. The autophagy-inhibitory effect of autophagy in HCC is mainly exercised through multiple mechanisms, genomic stability, and cell death in the tumor cells, and modulation of the immune response.

One of the main points contributing to the restraining tendency of autophagy on HCC is maintaining the integrity of DNA. Autophagy contributes to the degradation of extra and abnormal organelles and proteins that would otherwise be genetically unstable in case of malfunction. Likewise, autophagy eliminates these possibilities of genetic mutations, preventing cancer initiation and growth. Autophagy acts as a risk remover. Beyond the effect on the cell cycle, autophagy is induced directly, arresting the cell cycle in response to stress and preventing the proliferation of damaged cells that might create a tumor [11].

Autophagy also indirectly induces cell death of tumor cells via the autophagic cell death process, which is different from the process of apoptosis and necrosis. The massive autophagic consumption of cellular components marks this form of cell death. During this process, cellular demise occurs. The exact molecular mechanisms and conditions when autophagic death occurs are still under scrutiny,

but the potential usefulness of this method for cancer prevention can be shown. Apoptosis, together with the activation of the autophagy, destroys the cells. Nonetheless, it also means that autophagic cell death has the potential to become a modality for eradicating cancer cells uniquely [12].

Therefore, apart from this, autophagy has a crucial role to play in repressing imperfect immune reactions against tumors. Autophagy, as it carries out the failed antigens and the manner in which it releases immunomodulatory cytokines, could enhance the immune system's detection and elimination of cancer cells [13]. This is especially true for HCC, where the liver's unique immunological environment can determine the tumor's progress and the response to therapy. Autophagy is noted to be involved in the cross-presentation of tumor antigens to T cells, an endeavor that is pro-tumor immunity and halts the growth of HCC [14].

In the most recent studies, we have defined genes and pathways, such as autophagy, which controls HCC growth and spread through cancer cell extinction. For example, the PTGS-2 (prostaglandin-endoperoxide synthase gene) has demonstrated its role in regulating autophagy and pro-tumor lysis in hepatocellular carcinoma. Downregulation of PTGS-2 and those hub genes involved in autophagy decreases apoptosis, promotes HCC progression, and worsens prognosis. These results underline the level of autophagy participation in stopping tumor growth.

To conclude, the incident of autophagy rendering an HCC cell dormant by favoring genomic stability, initiation of cell death, and immune system modulation has been observed. Such evidence points out the possibility of aiming for the treatment of HCC.

3.3. Cross Talk between Autophagy and Apoptosis in HCC

Recently, the results of experiments have pretty much confirmed the roles of autophagy and apoptosis in the pathophysiology of HCC. For example, a particular study from the search results has a relation with non-apoptotic programmed cell death as well as the regulation of autophagy in HCC, therefore showing the relative complexity of these cellular processes. Another research discovered downregulated hub genes and key pathways related to HBV-HCC, suggesting immunosuppression, autophagy inhibition, increased probability of recurrence, and more malignant behavior of HCC, which may be the manifestation of a typical feature of decreased apoptosis and metastasis [15]. As this evidence demonstrates, manipulating autophagy as well as apoptosis regulatory types of machinery offers novel therapeutic opportunities in HCC.

In short, the Beclin-1/Vps34 complex and the importance of crosstalk between autophagy and apoptosis are distinct factors that modulate the course of HCC and its clinical management. The increasing research and development demonstrated by the studies and the exploration of the concept of autophagy have shown the potential of autophagy as an intervention. These crucial aspects suggest ways to develop treatment approaches that are more efficient and targeted to HCC and point out the significance of continued research in the field.

In recent years, the research has substantially empowered us to comprehend the dual role of autophagy in the development and progression of hepatocellular carcinoma (HCC), aiding cancer cell survival under stressful environments while also promoting its elimination. The discovery that autophagy induced by sorafenib, due to advanced HCC, resulted from the breakdown of genes at a molecular level. Scientists have provided indisputable chemical proof for autophagic mechanisms [16]. This study found that sorafenib triggered the autophagy induction via a SHP-1-STAT3-Mcl-1-Beclin 1 pathway, making a distinct connection between therapeutic intervention and autophagy induction in HCC cells. The study has shown the promising potential of using autophagic pathways as a therapeutic strategy in this disease for various reasons: the effectiveness of current treatments could be enhanced, and the development of new drugs could also be essential.

3.4. Presentation of Groundbreaking Studies and Known Consequences

Recent research has focused on the function of the Beclin-1/Vps34 complex, a main component of autophagy initiation that is crucial for HCC. The findings of Tai et al. concentrated on the role of this complex in the treatment of HCC, with the result that both sorafenib and SC-59 induced

autophagy through a pathway involving Beclin 1. This observation not only reinforced that the Beclin-1/Vps34 complex is vital for the induction of autophagy but also pointed to the therapeutic potential of developing therapy based on this complex against HCC [14]. Moreover, the investigators also elaborated on a combined phloretin-based treatment with glucose for regulating the role of autophagy genes in the HCC genetic setting, which might support new ideas for treatment. Evidence from such successful studies will not replace current treatment but will lead to more effective and personalized methods to treat patients with HCC.

4. Molecular Pathways Involved

Several key molecular pathways regulate autophagy's dual role in cancer, including the mTOR (mechanistic target of rapamycin) and AMPK (AMP-activated protein kinase) pathways. These pathways are central to controlling autophagy in response to nutrient availability and cellular energy status. In HCC, dysregulation of these pathways often occurs, contributing to the complex role of autophagy in tumor dynamics.

4.1. mTOR pathway

The mTOR pathway, a major negative regulator of autophagy, is frequently activated in cancer, including HCC. Activation of mTORC1 promotes protein synthesis and cell growth while inhibiting autophagy. However, under conditions of metabolic stress or treatment with mTOR inhibitors, autophagy can be induced, providing a survival mechanism for cancer cells [17].

4.2. AMPK pathway

Conversely, the AMPK pathway, which is activated by low energy levels, serves as a positive regulator of autophagy. AMPK activation can inhibit mTORC1, thereby inducing autophagy. In the context of HCC, AMPK-mediated autophagy can have both tumor-suppressive and tumor-promoting effects, depending on the stage of cancer and the specific metabolic conditions.

4.3. Beclin-1/Vps34 Complex

While researching, this complex's importance in autophagy initiation is established in the context of general cancer research. The interaction between Beclin-1 and Vps34 determines the nucleation phase of autophagosomes, which is one of the key steps of autophagy. A failure in the regulation of this complex in cancer, including HCC, can greatly affect cell survival, growth, and therapy outcomes. Upcoming studies investigating the role of the Beclin-1/Vps34 complex in HCC pathophysiology could be very important for introducing some new therapeutic techniques.

5. New Trends of Recent Research

The HCC tumor microenvironment (TME) represents an important factor for tumor progression and treatment, with autophagy playing a crucial role in cancer cells' survival and subsequent growth and metastasis. According to a study, the suppression of autophagic flux is particularly an essential factor for mediating the TME by HCC. Uncovering the close relationships between the functional changes of autophagy in HCC and its malignancy may lead to a new autophagy-targeted therapy for HCC patients, as mentioned in the study. The forthcoming realization of autophagy's modulatory role in the TME points out that a holistic understanding of effective targeted therapy in HCC should be one of the most critical aspects of cancer biology. The revelation of the role played by various autophagy regulators in TME has paved the way for developing separate therapeutic protocols and treatment of HCC through initiatives to target the disorder mechanism itself.

The porous relationship between the preclinical studies of the autophagy application in hepatocellular carcinoma (HCC) suggests expansion into the clinical use of autophagy-based therapy in treating cancer. These are instances of research in autophagy that provide a wide array of

information on aspects including mediating the tumor response to treatment, its relation to chemotherapy resistance, and whether autophagy manipulates treatments to provide an increase in the credentials of the existing therapies [18].

This area of research makes a particular case in suggesting that sorafenib-mediated killing of HCC cells can be fostered through its modulation of autophagy. Sorafenib, a cancer treatment medication intended to control or cure HCC, autophagy a bit in cancer patients. Preclinical studies have looked into decisive cell-autonomous and cell-non-autonomous roles of autophagy in tumor ability through cancer therapy action, installing autophagy in a complex role leading to the cancer outcome being decided by therapy.

Also, we need to stay focused on the link between autophagy research and chemotherapy resistance in hepatocarcinogenesis. Autophagy, detected as a process of mediation, developed resistance to chemotherapeutic agents. The usefulness of planimetric studies, which have presented the modulatory effects of autophagy on chemotherapy resistance in cancer cells, displays a possibility that the chemotherapy effect could be strengthened in HCC patients, hence providing insight into the effective mechanism to be used in modulating autophagy for chemotherapy response and higher efficacy rates. Along with those, numerous types of research were carried out by the use of autism disease-modifying agents that could remain unfair by CQ and HCQ in preclinical conditions. These studies have brought to the forefront how CQ/HCQ can substantially block autophagy pathways, boost cell death suicide, and cancer regression in several cancer types, including HCC. This type of study demonstrates the potential of autophagy modulation as a therapeutic measure that can be used to boost the effectiveness of various HCC therapies [19].

Moreover, many researchers have examined cannabinoids for their ability to influence the autophagy process at the cellular level- one of the critical ways that cells maintain homeostasis. Preclinical reviews have been shared about the action of cannabinoids in the cancer-curing process, consisting of both that on autophagy in hepatocellular carcinoma. In these studies, cannabinoids were able to induce the type of cell death in cancer cells, which is autophagy-based, and thereby, the new ways regarding cancer management have been highlighted.

5.1. Autophagy as a Biomarker: a Tool for Diagnosing and Predicting HCC

Autophagy is a conservation mechanism that leads to the elimination or reuse of intracellular compartments and substances and is of paramount importance in the development of HCC as well as in the treatment of the disease. The last works have emphasized the benefit of autophagy-related genes, lncRNA, and the potential to serve novel HCC biomarkers. One good example is the survey unveiled five autophagy-related, long-non-coding-RNA signatures, which can be expediently employed as a new prognostic indicator for HCC and imply the remarkable significance of autophagy in the progression and outcome of the Compiling existing data, a research paper on the quality of ARGs sheds light on the importance of this class of genes in predicting HCC prognosis, thereby suggesting that the novel CHAF1B gene to be tested as a relevant autophagy marker that could be used for HCC prognosis.

This set of findings suggested using the expression pattern of autophagy, the occurrence of autophagy, and autophagic signaling components as functions of a biomarker for HCC, which could help the early diagnosis and prediction of the outcome of these patients.

5.2. Summary of Clinical Trials on HCC Autophagy Mechanism Modifiers

As of now, clinical trials are studying the efficiencies and side effects of autophagy control and the progress of cancer cells. This early-stage clinical trial (Phase Ib/II), which investigated the promising potential of the compound ABC294640, an autophagy modulator, to treat patients with advanced HCC, highlights the ongoing efforts to integrate autophagy science into the clinical world [3]. Targeted therapy for HCC, aimed at understanding the dynamics of autophagy and using these patients to achieve the best for patients, is the goal of these clinical trials. These trials have been

anticipated with excitement, given their promise of introducing newer HCC therapeutic options with the potential of better results for the treatment of HCC.

5.3. Future Directions

Future research of HCC inquiry may involve finding other, more precise autophagy-related biomarkers that oversee the development of highly specific and less toxic novel autophagy modulators and the cloning of the mechanisms in the dual role of prevailing in cancer development. Identifying the intricate crosstalk between autophagy and other cellular pathways in the context of HCC progression is fundamentally significant as it will facilitate the generation of more effective cancer treatments.

The benefit of combining autophagy with other research on cancer, like immunotherapy targeted therapy, could make a comprehensive understanding of cancer biology and provide a space to develop a combination of therapies that would act against multiple at once. Therefore, an integrated approach can control the disease condition more effectively and may even lead to the discovery of new therapeutic agents for managing HCC.

Particular studies on autophagic modulation targeting indicate a positive outlook toward the personalized medicine human HCC treatment. The strict conformance to provide proof for specific molecular patterns of the patients, therefore, allows the therapies to be oriented to targeting individual characteristics of the patient's tumor, which has a better result with fewer side effects. The bright potential of individual collaborative medicine methods for HCC is embodied by their strong capability of altering how patients are treated. This strict precision in making medications using molecular inventions will benefit the existing treatment methods.

In the past few years, the description and investigation of autophagy processes in hepatocellular carcinoma (HCC), which is a type of cancer, massively increased our knowledge about the sophisticated cellular phenomenon and how it is related to cancer on the cellular level. Autophagy as a fundamental phenomenon was once confused to have dual roles in HCC - to be both the processes of cancerous cell survival from stress conditions and a possible therapeutic target. The discovery of autophagy-related genes (ARGs) and long non-coding RNAs (lncRNAs) as diagnostic and prognostic indicators among hepatocellular carcinoma (HCC) patients opened up overwhelming opportunities for preventive, diagnostic, and tailored treatment of HCC.

The breakthrough that is just being made in the field is inspiring to the experts. Now, the therapeutic purpose of autophagy pathways in HCC is achieving remarkable progress due to the research involved. The role of autophagy inhibitors in promoting HCC cell death has also been identified in some experimental model systems. However, further research is needed to evaluate their therapeutic potential as standalone anti-cancer agents or to be used in combination with other targeted drug modalities. Besides that, clinical trials are being conducted to search for autophagy regulators in HCC patients to implement the present results into the clinical practice that could be pivotal for alleviating patients with HCC [20].

Given the progress being made in autophagy research in cancer and other diseases, similar improvements may soon be seen in cirrhosis and HCC. In the context of the proposed study, the focus of potential future research would be on the direction of new autophagy biomarkers, the strain on the development of more specific and non-toxic autophagy drugs, and the understanding of the vaccination mechanism of the two-sided effect of autophagy. As it is clear that autophagy alone cannot cure cancer, it should be integrated with other cancer research areas to form a paradigm shift in drug development for cancer treatment.

6. Conclusion

HCC is caused by prolonged liver damage and inflammation-induced fibrosis and cirrhosis. To conclude, investigation in the field of autophagy in HCC research is quite innovative and has the potential to culminate in life sciences. The strides already taken in this journey are immensely

significant, so hope for improved, better, and customized treatments of HCC in the future is active. With each progress in the study of autophagy in the setting of HCC, the luminous opportunity of advancing the treatment of cancer does not disappear, thus underlining the always essential direction for the researchers who study this field.

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