Autophagy in Breast Cancer is a Powerful Regulator of Tumour Growth and Therapeutic Response

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Abstract

Breast cancer is a terrible illness that has caused a drop in women's life expectancy and has a high morbidity and mortality rate. The most frequent malignancy in women is breast cancer, which has traditionally been treated with surgical removal, chemotherapy, and radiotherapy. Breast tumours exhibit altered biological behaviour due to genomic and epigenetic alterations, depletions, and dysregulation of molecular processes, including autophagy. When autophagy has a pro-death role, it reduces the viability of tumour cells. Autophagy function can be oncogenic in enhancing cancer. The carcinogenic role of autophagy in breast tumours is a barrier to patients receiving successful therapy since it can result in radio- and medication resistance. Autophagy can control key breast tumour characteristics such glucose metabolism, proliferation, apoptosis, and metastasis. Oncogenic autophagy can prevent apoptosis while encouraging breast tumour stemness.Moreover, autophagy exhibits interaction with elements of the tumour microenvironment like macrophages, and its level can be controlled by anti-tumor drugs in the treatment of breast tumours. The pleiotropic function of autophagy, its dual rol (pro-survival and pro-death), and its interplay with crucial molecular pathways like apoptosis are grounds to take it into consideration in the treatment of breast cancer. Also, the present review offers a pre-clinical and clinical assessment of autophagy in breast tumours.

Keywords: Breast cancer • Chemotherapy • Auto phagy • Apoptosis • Proliferation

Introduction

According to data released in 2020, breast cancer incidence rates are now higher than lung cancer incidence rates worldwide, and management of the disease in women looks to be particularly important given its high prevalence and aggressive character. Breast tumours can be classified as luminal A, luminal B, HER2 +, and basal-like triple negative breast cancer based on histological features. The intricate breast TME and the existence of several cell types, including immune cells, T cells, NK cells, tumor-associated macrophage, and plasma cells, have contributed to the progression of breast cancer, and clinical attempts to identify the involvement of the TME have been made. Breast cancer cells exhibit significant central nervous system metastasis, which is thought to be a risk factor for patients and lowers their prognosis and survival rate. Recurrence of breast cancer is a concern as well, and elements contributing to this mechanism should be clarified in order to treat patients effectively. Overall, breast cancer exhibits heterogeneity, which has made it challenging to choose an effective therapeutic strategy. It has been demonstrated that the presence of distinct subpopulations with varying characteristics has affected the ability of breast tumour cells to metastasize and their refractoriness to treatment. As solid biopsy excludes additional cancer-related alterations, it is no longer the best method for revealing information about the complete tumour. As a result, liquid biopsy is used as a potential method to diagnose tumours and find circulating tumour cells. The presence of circulating tumours in cancer patients' blood, especially breast cancer patients, is a benefit. Although radiotherapy, chemotherapy, and immunotherapy have been used as therapeutic options, it is a fatal disease in women. Due to its capacity to reduce the rate of proliferation and raise therapeutic sensitivity, gene therapy has been adopted in the treatment of breast tumours. Use of nanobiotechnology for therapeutic agent delivery, precise targeting of breast tumour cells, and lowering their viability is another possibility for treating breast cancer. Additionally, by causing cell death and boosting chemo-sensitivity, naturally occurring substances like curcumin and quercetin can be used to treat breast tumours. Controlling autophagy and apoptotic cell death is crucial. The endoplasmic reticulum, mitochondria, and other organelles all play a role in apoptosis induction, which has a significant impact on survival rates. Increased carcinogenesis and therapeutic resistance are both mediated by EMT induction. A recently identified process in cancer with a context-dependent function is autophagy. Inducing autophagy can be helpful in slowing the growth of tumours, and when it has a pro-survival function, it can also increase the viability of cancer cells. Autophagy is a physiological mechanism for maintaining homeostasis and regulating physiological processes. In order to maintain cellular homeostasis, microorganisms like viruses and bacteria, damaged organelles, and proteins can be destroyed by autophagy using the lysosomal and proteasomal machinery. The way the autophagy apparatus is delivered to the lysosomes differs between macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy, the most common type, involves the production of autophagosomes. The production of phagophore is a characteristic of the autophagy start stage. The phagophore membrane expands during the second phase, known as elongation, which leads to the subsequent engulfment of cytoplasmic cargo and the formation of the autophagosome, also referred to as the autophagic vacuole and a double-membraned structure. When an autophagosome is produced, its fusion with a lysosome results in the degradation of the cargo with the aid of enzymes like cathepsins and acid hydrolases. The contents of the cargo are released into the cytoplasm for disintegration after being enclosed by autolysosomes. There are many acknowledged regulators of the autophagy pathway in cells. In situations where energy and amino acid levels are low, such as famine, the mTORC1 complex is inhibited and it manifests freely in the cytoplasm, rendering it incapable of controlling the autophagy mechanism. Nevertheless, contacts between lysosomes and their cell membrane cause activation of v-ATPase, which recruits mTORC1 for autophagy suppression, when energy and amino acid levels are high. In order to induce autophagy, a complex made up of ULK1/2, Beclin-1, and VPS34 must be present. It inhibits ULK1/2 to suppress autophagy once mTOR signalling is activated. By overexpressing LC3B, a protein involved in phagophore elongation and autophagosome formation, ULK1/2 is involved in triggering autophagy. By phosphorylating UVRAG, upregulating mTORC1 can also prevent the fusion of lysosomes and autophagosomes. Such connections introduce into biosynthetic pathways and control autophagy in cells. The role of autophagy in regulating other cell death mechanisms and other functions has recently attracted attention, and studies have also sought to unravel the molecular mechanisms controlling autophagy. When apoptosis is triggered by the TRAIL, autophagy proteins are able to be recruited to the death machinery. Together with apoptosis, autophagy including several sorts of pathways like TMEM164, GPX4, and HPCAL1 can also regulate ferroptosis, another

type of death mechanism. Dysregulation of autophagy proteins can be a mediator of diseases in humans since autophagy is a crucial regulator of cell homeostasis. Autophagy has an interesting role in the field of immuno-oncology because it facilitates the immune system's communication with the body and because of its dual role in the induction and repression of anti-cancer response. The research of autophagy in oncology is intriguing due to the high mortality rate from cancer, and the complexity of autophagy's role has made cancer therapeutic targeting difficult. Also, it has been thought that targeting autophagy for cancer therapy through medication repurposing is attractive. It's interesting to consider how cancer affects the autophagy system and how to modulate it for treatment. Suppression of PIKfyve and p38MAPK pathways reduces autophagy and decreases protein breakdown by autophagy in lowering development of tumour cells As one of the upstream mediators of autophagy, HUVE1 causes ubiquitination and ATG101 degradation to limit autophagy, leading to a marked decrease in viability rate. PITX2B is a lung tumour carcinogen, and its overexpression encourages survival and development. When PITX2B is knocked down, autophagy and apoptosis are induced, which slow the growth of lung tumours. The link between autophagy and therapeutic resistance is interesting since it is crucial for successful treatment. Radio-resistance in tumours is stimulated by REV1 down-regulation, and this is linked to the induction of autophagy. Autophagy activation is thought to be the cause of colorectal carcinoma cells' treatment resistance. In order to drive autophagy and advance colorectal tumour growth while protecting cancer cells from harm and inducing chemo-resistance, IL-6 induces JAK2 signalling and enhances BECN1 expression. ATF4 down-regulation is advised to prevent pro-survival autophagy via mTOR up-regulation in addition to glutaminolysis suppression. These results suggest that autophagy can control how tumour cells react to anti-cancer medications. Autophagy also exhibits connections with other forms of death, such as apoptosis. Autophagy regulation in cancer is regulated by a number of signalling networks, including Sonic Hedgehog signalling, which is a promising factor in tumour suppression.

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