DNA Repair 98 (2021) 103032

Contents lists available at ScienceDirect

DNA Repair

journal homepage: www.elsevier.com/locate/dnarepair

DNA damage response and breast cancer development: Possible therapeutic applications of ATR, ATM, PARP, BRCA1 inhibition

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ARTICLE INFO

Keywords:
Autophagy
Beclin-1
ATG
Breast cancer
DNA repair

ABSTRACT

Breast cancer is the most common and significant cancers in females regarding the loss of life quality. Similar to other cancers, one of the etiologic factors in breast cancer is DNA damage. A plethora of molecules are responsible for sensing DNA damage and mediating actions which lead to DNA repair, senescence, cell cycle arrest and if damage is unbearable to apoptosis. In each of these, aberrations leading to unrepaired damage was resulted in uncontrolled proliferation and cancer. Another cellular function is autophagy defined as a process eliminating of unnecessary proteins in stress cases involved in pathogenesis of cancer. Knowing their role in cancer, scholars have tried to develop strategies in order to target DDR and autophagy. Further, the interactions of DDR and autophagy plus their regulatory role on each other have been focused simultaneously. The present review study has aimed to illustrate the importance of DDR and autophagy in breast cancer according to the related studies and uncover the relation between DDR and autophagy and its significance in breast cancer therapy.

1. Introduction

Breast cancer is the most common malignancy in females with an estimated incidence of more than 1.5 million cases annually [1,2]. Based on the stage of tumor, conventional therapy has been performed consists of hormone therapy, surgery, and chemotherapy with anthracyclines, Taxanes and other agents and radiotherapy. New approaches have been recently emerged in the field of breast cancer treatment such as immunotherapy and targeting specific cellular signaling pathways. The immergence of these new therapies is justified by rather low survival rate of cancers diagnosed in later stages and the recurrence of tumors even in earlier stages and their resistance to conventional therapies [3,4]. Multiple etiologies have been suggested as the main culprits of resistance including changes in absorption, activation and metabolism of anti-cancer agents, inhibition of apoptosis and increased DNA repair [5]. One important cellular signaling pathway involved in acquisition of resistance is DDR pathway. One of the main mechanisms of chemotherapy agents' action is damaging the DNA content of cells which is resulted in apoptosis via changes in the balance of pro and anti-apoptotic proteins. DDR is operated by various molecules able to recognize the damage implicated by chemotherapy agents and induce DNA repair, then neutralizing the effect of anti-cancer agents [6]. Another major method of acquiring resistance is the activation of autophagy. Studies have shown that multi-resistant cancer cells have a

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https://doi.org/10.1016/j.dnarep.2020.103032
Received 7 October 2020; Received in revised form 6 December 2020; Accepted 7 December 2020
Available online 17 December 2020

higher detectible rates of autophagy [7]. Autophagy enables the cell to recycle unnecessary particles and organelles, making it more resilient in stressful conditions. Autophagy is regulated via molecules, such as PI3K-Akt-mTOR pathway, Bcl-2, Beclin1, Ras and p53. Interestingly, most of these regulators are also effectors in cascade of DDR [8–10]. Thus, it has been suggested that DDR and autophagy could be functionally overlapped and can even work in conjunction in order to facilitate the coping process of cell [11,12]. The effectiveness of targeting DDR and autophagy in breast cancer cells has been recently shown [13]. Accordingly, in this study, the significance of DDR and autophagy in breast cancer have been discussed beside the evaluation of their therapeutic implications and the possibilities arising from targeting their overlaps in cancer therapy.

2. DNA damage and DNA damage response in breast cancer

DDR composed of multiple molecules and acting in conjugation to sense DNA damage activates transducers in turn with the mediatory function of other molecules activate effector molecules. Based on damage degree and characteristics of cell, effectors can initiate DNA repair process and induce cell cycle arrest, apoptosis or senescence [14,15]. The first step in DDR is the sensing of damage via two major pathways including ATM pathway which senses double strand breaks (DSBs) and ATR pathway which senses single strand DNA sequences [16,17]. MRE11, RAD50 and NBS1 (MRN) complex act as a sensor in ATM pathway and RPA and RAD9-RAD1-HUS1 complex act in conjunction with RAD17 senses damage in ATR pathway [18]. It has been shown that aberrations in DNA damage sensing could be a culprit in breast cancer. Bartkova et al. has shown that in a population of almost 1000 patients, 3%, 7% and 10 % have a reduced level of RAD50, MRE11 and NBS1. This reduction in expression level has been accompanied with specific histopathologic findings showing that it is associated with negative estrogen and progesterone receptor. Tumors with reduced RAD50 are shown to be more of ductal origin compared to ones with normal RAD50 levels [19]. γ-H2AX is another DNA sensor involved in breast cancer. Constitutive γ-H2AX staining is associated with triple negative breast cancer and BRCA1 mutations [20–22]. According to the active pathway, when damage is sensed, the sensors activate the transducer molecules (ATM and ATR) which in turn activate the downstream CHK2 and CHK1, respectively. In these components of DDR cascade, aberrancies have shown to be significant in breast cancer. Studies have shown that genetic variants of ATM could be associated with breast cancer [23]. Hyper-methylation of ATM promoter is shown to be a biomarker of breast cancer [24]. Also, different variations in the expressions of ATM/BRCA1/RAD51 are related to the prognosis of breast cancer patients [25]. Likewise, ATR and its involvement are proved in breast cancer. A study performed by Lin et al. has found that single nucleotide polymorphisms of ATR and CHEK1 could be associated with breast cancer [26]. More definite evidence regarding ATRs involvement in breast cancer is elicited by Wang et al. showing that ATR mutant rs13091637 is associated with breast cancer [27]. The next groups of molecules involved in the pathogenesis of breast cancer are the mediators of DDR. One of these mediators is 53BP1. It was shown that this molecule acts as a potential tumor suppressor by inhibiting NF-κB pathway through miR-146a [28], suppressing epithelial mesenchymal transition by recruiting microRNA-200b/429 to downregulate ZEB1 [29] and inhibiting angiogenesis in breast cancer [30]. Similar roles exist for another mediator of DDR as the Mediator of DNA damage checkpoint protein 1 (MDC1) [31,32]. As mentioned earlier, the combined effect of signaling initiated by DNA damage, sensed and conveyed to downstream effector molecules is to initiate one of the end points of DNA damage. One end point is DNA repair, then studies have illustrated that malfunctioning DNA repair is a culprit in progression of breast cancer [12]. The next end point is the induction of apoptosis. Disturbance of balance between pro-apoptotic and anti-apoptotic molecules is a driving force in breast cancer, enabling malignant cells to proliferate without a hurdle contributed to an increased tumor load and new mutation accumulation [33]. Distribution of cell cycle and its protective role against uncontrolled cellular proliferation is similarly related to breast cancer [34].

3. Targeting of DDR as anticancer therapy in breast cancer

Targeting DDR is shown to be effective in multiple cancers like breast cancer [35]. As mentioned before, DDR has multiple components that all of them could be a possible target for cancer therapy [18]. A study conducted by Flores-Perez et al. has found that targeting of RAD50 (a component of MRN complex via interfering RNAs) is able to sensitize previously resistant breast cancer cells to cisplatin and other platinum agents [36,37]. The same effect is seen in MRE11 (another part of MRN) which is down regulated via FGFR2. This is mediated via two molecules as POU1F1 and ERK. ERK (a downstream molecule of FGF signaling) phosphorylates POU1F1 and increases its binding to the promotor of MRE11 gene. This interaction leads to the disruption of DDR in breast cancer cells and sensitizes cells to chemotherapy by inhibiting the initiation of double strand break repair [38]. H2AX can also be a target for therapy in breast cancer. A study by Shin et al. has found that actin disruption agents are able to induce the phosphorylation of H2AX, causing G2 arrest and apoptosis in MCF-7 cells hypothesizing that this particular mechanism could be a target for cancer therapy [39]. Targeting the RAD17 shows a clinical significance in breast cancer. Zhou et al. has found that stabilization of RAD17 (by interfering in Cdh1/APC pathway) could sensitize breast cancer cells to various drugs, the disruption interfered with DNA repair is initiated via DDR after chemotherapy [40].

ATM as one of the junction points of DDR with important cellular pathways, such as PI3K-AKT, MEK-ERK is an effective target in breast cancer [41]. A study by Zhang et al. has shown that zinc finger E-box binding homeobox 1 (ZEB1) induces resistance to epirubicin (a chemotherapy agent) by forming a complex with p300 and PCAF on the promotor region of ATM led to the expression increment and subsequently increased rates of homologous recombination [42]. Activation of ATM resulted in cellular arrest in G2/M of MCF7 cells under goes treatment with Artesunate [43]. This effect is also shown with the administration of Pectenotoxin-2 [44]. Huaier extract is to induce cellular arrest, but in G0/G1 interval by increasing ATM via the inhibition of miR-203 [45]. Another important utility of targeting ATM is its importance in the efficacy of poly (ADP-ribose) (PARP) inhibitors. A study by Gilardiniet al. has shown that reducing the levels of ATM in cancer cells is able to increase the sensitivity to PARP inhibitors in MCF-7 and ZR-75-1 cell lines [46]. ATR is also shown to be a possible target for therapy. Different studies have shown that ATR inhibitors such as AZD6738 and NU6027 are able to induce cellular arrest in G2/M and increase sensitivity to platinum agents and PARP inhibitors [47]. The use of ATR inhibitors is shown in targeting specific cell lines of breast cancer for personalized therapy. Cell lines with low nuclear phosphate and tensin homolog (PTEN) are shown in higher grade and high proliferation. The use of VE-821(a chemical compound that inhibit the phosphorylation of ATR and Chk1 and strongly induce activation of H2AX) causes an accumulation of DNA damage resulted in increased apoptosis [48]. Another use of ATR inhibitors is in the combination therapy with other inhibitors of molecules involved in DNA damage. This is shown in a study by Jin et al. in which the combined use of AZD1775 (a WEE1 inhibitor) and AZD6738(an ATR inhibitor) are shown to be effective in triple negative breast cancer [49]. In another study, IGF-1R inhibitor BMS-754807 and ATR inhibitor VE-821 are used in the combination of MCF-7-R cell lines [50]. One of the molecules related to the function of ATR is ATR interacting protein (ATRIP) including an important role in establishing a bond with BRCA1. The substitution of SER (239) with alanine in this molecule has caused G2/M defect. This interaction inhibits the direct interaction between BRCA1 and ATRIP that is vital for the checkpoint activity of ATR [51]. The

downstream molecules of ATR and ATM, CHK1 and CHK2 are the next discussed targets. CHK2 is involved in the function of Bisacylimidoselenocarbamates. These agents cause G2/M arrest in breast cancer cells and one important mechanism of their function is targeting CHK2 and CDK1 [52]. Further, the inhibitors of CHK1 show promise in breast cancer. MK-8776 is one of these agents showing the radio-sensitivity increment in triple negative breast cancer cell lines of MDA-MB-231, BT-549 and CAL-51, while acting in conjunction with doxorubicin on p53-deficient breast cancer cells [53,54]. AZD7762 is another inhibitor able to sensitize p53 mutant cell lines to radiation showing an increase in radiation induced γH2AX expression [55,56]. The same results are shown in a separate study performed by Zhang et al. in which AZD7762 has significantly inhibited the replication of breast cancer cells and increased the killing of these cells [57]. Also, Ma et al. has shown that two CHK1 inhibitors (UCN-01 or AZD7762) are able to induce apoptosis in triple negative breast cancer cell lines [58]. Mediators of DNA damage have also been targeted in breast cancer. The most important mediator of DDR targeted is BRCA1. A study by He et al. has shown that restoring the expression of miR-218 that reduces the levels of BRCA1 is able to increase the sensitivity to cisplatin in MCF-7/DDP cells [59]. miR-185 is also able to reduce the proliferation of breast cancer cells by targeting DNMT1 and E2F6 which was led to the increased BRCA1 levels [60]. As mentioned before, PARP inhibitors are a group of medication with the most efficacy in cell lines deficient in DSBs [61]. In this case, the depletion of BRCA1 is able to render cell susceptible to PARP inhibitors. This finding is significant because most sporadic breast cancers are those with intact BRCA1/2 and DNA repair [62]. The end of DDR leads to DNA repair, checkpoint activation and cellular arrest, apoptosis or senescence. Targeting DNA repair has been progressed in a way that personalized therapy should be initiated based on aberrations in DNA repair genes. Examples are target in nucleotide excision repair (NER) deficient cells with doxorubicin. Based on recent research, cell lines with mutation in XPD are more sensitive to treatment with doxorubicin or targeting DSB by taxanes for this purpose. Taxanes downregulate BRCA1 and this downregulation leads to complete deficiency in DSB repair. As a result, accumulation DSB leads to death in cancer cells [63]. Cell cycle proteins can be targeted by silencing RNAs causing arrest in cell cycle or activating other end points such as apoptosis. In a study by Parmaret al., dicer-substrate siRNA is used to target CDC20 causing an inhibition in growth [64]. Other studies have examined the effect of blocking cycle dependent kinases such as CDK 4/6. It is hypothesized that agents such as palbociclib, ribociclib, and abemaciclib used in blocking of these CDKs are able to induce cellular arrest in G1 and counter one of the frequent mutations observed in breast cancer [65]. Apoptosis is defined as the programmed death of a cell which is accumulated much to damage and able to sustain a normal existence. Some studies have tried to induce apoptosis in breast cancer by various agents ranging from chemotherapy agents, polyphenols, vitamin C and more [66,67] In addition, studies have shown that inducing senescence could be a novel strategy in battling cancer. Salinomycin is able to induce apoptosis and senescence in breast cancer MCF-7, T47D and MDA-MB-231 cells [68].

4. Functions of autophagy in breast cancer

Autophagy is a process in which unnecessary particles of cell are degraded in instances of cellular stress. Based on multiple *in vitro* and *in vivo* research initiatives performed on autophagy, it is understood that this function is performed in multiple steps including induction of autophagy, creation of phagophore and autophagosome, fusion of autophagosome with a lysosome and degradation of newly formed autolysosome's contents and finally reuse of micro-molecules resulted from the degradation process [69]. Regulation of autophagy is mainly done by mTOR as a negative regulator and AMPK as a positive regulator [70]. These two molecules directly affect the activation of a serine threonine kinase complex composed of ULK1&2. ULK complex is then relocated to a specific location on the endoplasmic reticulum which is marked by ATG9 [71]. The next step is the recruitment of class III phosphatidylinositol 3-kinase complex composed of PIK3C3/VPS34, PIK3R4/p150, BECN1/ Beclin-1 and ATG14 [72]. After this step, Golgi complex can have complementary roles in expanding phagophore [73]. Mitochondria-associated membranes (MAMs) have an important role in the closure of phagophore and creation of phagosome by localizing ATG complex activity [74,75]. The next step is the fusion of autophagosome with lysosome which is mediated by wide arrays of molecules including HOPS family of molecules, RAB7, adaptors molecules such as EPG5 and SNARE family molecules. The collective action of mentioned molecules ensures specificity in lysosome function [72]. Regarding the significance of autophagy in cancer, numerous studies have shown both pro and anti-neoplastic roles for autophagy. Induction of autophagy enables cancer cells to better cope with the harsh tumor microenvironment which is loaded with wastes and low in oxygen and nutrients. Autophagy is one of the reasons that cancer cells are able to cope with the damage(s) caused by chemotherapy agents including dose affecting the integrity of a cell's DNA. However, autophagy can also be utilized as a method to induce cellular death via an apoptosis-independent process [8,76]. Studies regarding breast cancer have shown that autophagy has a key function in the progression, malignant transformation, survival, metastasis and chemo-resistance of breast cancer cells [77]. Probably the most rigorously result of autophagy in breast cancer is resistance to treatment. It is demonstrated that hypoxia is able to increase the formation of autophagosomes and to increase the induction of m-RNA of certain molecules such as Beclin-1, Atg5, Atg7 and Atg12 in breast cancer. Cells treated with hypoxia are shown to have an increased resistance towards ionizing radiation. This is proved when a siRNA targeted to Beclin-1 is able to re-sensitize these cells to radiation [78]. Another study by Sun et al. has found that MCF-7er and SK-BR-3er cells resistant to epirubicin and paclitaxel are able to avoid apoptosis via initiating autophagy [79]. Huang et al. has declared that autophagy facilitated cancer cells escapes from apoptosis by inducing senescence in PTTG1-depleted cancer cells. Based on the observation in this study, though the induction of autophagy helped cells avoid apoptosis, it also prevents the initiation of bystander effects of senescence which are mediated by Senescence-associated secretory phenotypes(SASPs). It is shown that CSF2-JAK2 pathway has an essential role in regulating these functions [80]. Besides the chemotherapy agents, inhibitors of specific cellular pathways such as PI3K pathway are used in breast cancer, especially estrogen receptor positive breast cancer. Yang et al. has found that inhibiting autophagy by Chloroquine has potentiated the effects of PI3K inhibition led to mitochondrial membrane depolarization and apoptosis [81]. Despite its unknown affecting mechanism, autophagy has roles in sensitivity to hormone treatment in estrogen positive breast cancers [82]. Another important significance of autophagy in breast cancer is its prognostic value in foretelling recurrence [83]. Vera-Ramirez et al. has found that one important mechanism of dormant breast cancer cells utilized to sustain themselves after treatment is autophagy. ATG7 has an essential role in this regard. Inhibition of autophagy in these cells has significantly decreased the metastatic burden of these cells by an accumulation of mitochondria damage and reactive oxygen species [84]. Also, though the transient blockade of autophagy has increased dormancy, knockdown of ATG5 resulted in permanent autophagy inhibition has reduced the dormant period of cells. Furthermore, cells with non-functional ATG5 are sensitized to immunotherapy [85]. Another study has found that downregulation of ATG5 has resulted an increased rate of metastasis [86]. The relation between the immune system and autophagy is also shown in a study by Ladoire et al. in which breast cancer cells with positive LC3B has an increase ratio of CD8(+) cytotoxic T lymphocytes to local FOXP3(+) regulatory T cells and tumor associated macrophages [87]. Further, Akalay et al. has proposed that autophagy coupled with epithelial to mesenchymal transition could act as a way of avoiding T-cell-mediated lysis [88]. Multiple studies have also shown that autophagy related genes are differently expressed in different kinds of breast cancer. Choi et al. has found that the expression

of LC3A, LC3B and beclin-1 is higher in triple negative breast cancer compared to other types of cancer [89]. Chen et al. has reported that these variations are prognostic value due to the fact that there is a significant relation between LC3B levels and relapse free survival and overall survival [90]. Chang et al. has demonstrated similar results in triple-negative breast cancer. They found that the reduced expression of LC3 and stemness (CD44+/CD24-/low) indicate a highly aggressive tumor subtype [91]. Wang et al. has found that the expression levels of ATG5 and FIP200 are significantly related to disease free survival in more than 200 specimens of breast cancer [92]. Ueno et al. has investigated the expression of Beclin-1 in cancer cells undergoing treatment with exemestane and found that the status of Beclin-1 is associated with higher proliferation after treatment and poor clinical outcome [93]. Autophagy is also sought to be an initiating factor in the emergence of breast cancer. Multiple studies have shown that cancerous tissue have reduced the expression of LC3-II and Beclin-1 compared to normal tissue, also up to 50 % of breast cancers have deletions in BECN1 gene [94]. It was shown that autophagy in cancer associated fibroblasts can enhance the migration and proliferation, invasion and transformation of triple negative breast cancer partially by affecting Wnt/β-catenin pathway [95,96]. Further, autophagy has an important role in the metabolism of malignant cells. It is well understood that autophagy enables cells to survive in hypoglycemic states. This is mediated by the degradation of p62 which sequesters KEAP1 and allows the perseverance of Nrf-2 [97]. Autophagy has a role in yielding resistance against tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in breast cancer. This is shown in a study by Lv et al. where MDA-MB-231 cells resistant to TRAIL shows higher levels of lapidated LC3B and decreased p62/SQSTM1 expression [98]. Autophagy also has important roles in the regulation of breast cancer stem-like cells by affecting EGFR/Stat3 and TGFβ/Smad signaling pathways [99].

5. Targeting of autophagy as anticancer therapy in breast cancer

As mentioned before, many roles of autophagy in cancer development have led to target molecules involved in its process. Multiple trials targeting cancers such as pancreas, colon, respiratory system and glioblastomas have shown mixed results [100]. In this regard, various agents have been utilized in suppressing autophagy consisting of hydroxychloroquine (HCQ) and 3-Methyladenine, Wortmannin and LY294002 (recently introduced agents) which all inhibit autophagy by inhibiting PI3-kinase, SBI-0206965 a ULK1 Inhibitor, Spautin-1 a USP10 inhibitor, SAR405 a Vps18 and Vps34 inhibitor, NSC185058 an ATG4 inhibitor and others such as ROC325 and Lys05 with an unknown mechanism of action [101]. Apart from these agents specifically known to affect autophagy, multiple other agents with functions in other cellular pathways, such as PI3K signaling, ERK signaling, NF-κB signaling and Wnt/β-catenin signaling are shown to affect autophagy (Table 1). Accordingly, these agents highly affect different breast cancer cell lines by affecting autophagy from sensitizing previously resistant cell lines to treatment causing apoptosis or autophagy dependent cell death inducing cell cycle arrest, increasing or decreasing (dependent on cell line) the period of dormancy an anti-cancer effects on cancer stem cells [102].

6. The interaction between autophagy and DDR in breast cancer

Obviously, there is a definite complicated relation between autophagy and DNA damage response mechanisms (Fig. 1). It was shown that autophagy can regulate DDR by affecting the expression and function of multiple key molecules involved in the process of sensing and modulating DNA damage [103]. One of these molecules is CHK1 which is active in the early DDR phases. Studies have shown that chaperone mediated autophagy has an important role in post-DNA repair period of DNA damage and that degradation of CHK1 by autophagy is necessary for the normal progression of cell cycle after DNA damage [104]. Further, autophagy is able to directly and indirectly regulate the process of DNA repair by affecting the expressions of molecules such as XPC active in NER or by regulating the balance between homologous recombination (HR) and non-homologous end joining (NHEJ) [105]. Liang et al. has performed a study for substantiation link between autophagy and DNA repair, resulting that chloroquine (an autophagy inhibitor) resulted in the accumulation of γ-H2AX (a marker of DNA damage) and inhibited HR are shown by a reduced amount of RAD50 and 51 [106]. Similar results in the importance of autophagy in regulating DNA damage are shown in a study by Nagelkerke et al. where PERK/ATF4/LAMP3 signaling is inhibited. This signaling pathway is an unfolded protein response which has important interplays with autophagy [107]. The inhibition of this signaling pathway has made radio-sensitized MDA-MB-231 cells to radiotherapy. Further, investigations have shown that the inhibition of PERK/ATF4/LAMP3 is accompanied by reduced γ-H2AX foci that means a decrease in DNA damage response [108]. A study by Bae and Guam has found that the inhibition of autophagy by FIP200 deletion (which is a FAK-family interacting protein required for autophagosome formation) could impair DNA repair and reduce the tolerance to etoposide treatment as DNA damage inducing chemotherapy drug [109]. A study by Karantza-Wadsworth et al. has studied the effects of autophagy on breast cancer cells undergoing metabolic stress and found interesting results. Beclin-1 is an essential autophagy regulator Allelic loss of Beclin-1 occurred in breast cancer led to DNA damage genomic instability, which is accompanied with enhanced tumorigenesis if it was coupled with a positive BCL-2 [110]. More than DNA repair, autophagy can interact with other end points of DDR such as senescence. A study by Goehe et al. has shown that senescence and autophagy with near identical regulatory signals (shown in an experiment) are the ROS generation caused by the use of Adriamycin suppressed by NAC, also ATM, p21, and p53 are modulated which is resulted in the inhibited autophagy and senescence. Further, intervening in autophagy with chloroquine is able to reduce and delay senescence, even if couldn't completely stop it [111]. Similar results are found by Capparelli et al. in which CDK inhibitors induce senescence and autophagy in MDA-MB-231 cells. Furthermore, the use of cell cycle inhibitors such as PD0332991 resulted in both autophagy and senescence has prompted the hypothesis that these two functions are biologically linked [112]. More evidence regarding the interplay of autophagy and senescence and their combined role in breast cancer has been emerged in cancer studies associated with fibroblasts. Alternatively, fibroblasts transfected with autophagy genes (BNIP3, CTSB or ATG16L1) have shown a unique set of characteristics encompassing autophagy and senescence called the autophagy-senescence transition (AST) (increased p21 and emergence of β-galactosidase as a marker for senescence). Injection of these cells would promote metastasis in breast cancer specimens by paracrine production of energy by mitochondria [113]. Another study has shown that the induction of autophagy and senescence leading to tumorigenesis could occur via the modulation of HIF-1 [114,115]. Despite the connection between tumor suppression and autophagy, based on the significant evidence showing the requirement of autophagy for proliferation in cancer, another study by Brown NE has unraveled the complex relation between autophagy and senescence. It is approved that cyclin D1 has an oncogenic property and its upregulation leads to tumorigenesis, targeting the cyclin D1, also the abrogation of its activity is therapeutic strategy. It is shown that cancer proliferation is increased in a response to knockdown of cyclin D1. This finding is correlated with upregulation of autophagy and down regulation of senescence, showing that there is likely a relation between autophagy and senescence induced by oncogenesis [116]. In contrast, DDR plays an integral part in the regulation of autophagy. As mentioned earlier, autophagy is mostly regulated by the actions of mTOR and AMPK signaling. DNA damage can have significant effects on both of these. When DNA damaging is sensed by sensors such as MRN complex, ATM is activated. Thus, based on the activated downstream, signaling can enhance autophagy [11]. A study

Table 1
Targeting of autophagy as anticancer therapy in breast cancer.

Cell line	Agents Used	Effect on autophagy	Type of study	Results	Ref
MDA-MB-231	[6]-gingerol	Increase	*In vitro*	Autophagy resulted in induction of caspase-independent apoptosis	[111]
MCF-7 and MDA-MB-453	miR-92b	Increase	*In vitro*	Inhibition of cancer cell viability, invasion and migration	[112]
4T1	anthracyclines and anti-CD47 therapy	Increase	*In vitro*	Enhancment of immune cytotoxicity and increased response to doxorubicin	[113]
MDA-MB-231 and MCF-7	SB02024	Inhibit	*In vivo*	Increased potency of Sunitinib and Erlotinib	[114]
MDA-MB-231, MCF-7, A549, SMMC-7721, Eca109, HEB and MCF-10A	Eight flavonoids from T. kirilowii	Increase	*In vitro*	Inhibited cellular proliferation and induction of apoptosis	[115]
MCF-7 and MDA-MB-23	Quercetin	Increase	*In vivo*	Inhibition of cancer cell migration and proliferation was achieved by targeting the Akt-mTOR pathway	[116]
MCF-7	3β,11-dihydroxy-9,11-secogorgost-5-en-9-one	Increase	*In vitro*	Generation of ROS and Apoptosis was increased	[117]
MCF-7 and MDA-MB-23	circ-DNMT1	Increase	*In vitro*	circ-Dnmt1 resulted in the relocation of p53 to the nucleus which resulted in increased autophagy. Further circ-DNMT1 decreased p53 expression	[118]
MCF-7	Corilagin	Increase	*In vitro*	An increase in apoptosis was seen, coupled by an increase in autophagy as a defense mechanism in cancer cells	[119]
MDA-MB-231	Flightless-I	Inhibition	*In vivo* and *in vitro*	Flightless-I blocked the recognition of LC3 by effecting p62	[120]
MDA-MB-231 and MCF-7	Nimbolide	Increase	*In vitro*	The increase in autophagy is mediated by an increase in Beclin-1 and LC3B and a decrease in p62 and mTOR	[121]
MDA-MB-231	miR-489	Inhibition	*In vitro* and *in vivo*	Inhibition of apoptosis resulted in increased sensitization to doxorubicin	[122]
MDA-MB-453 and BT474	Delphinidin	Increase	*In vitro*	Induction of autophagy was the result of the inhibition in mTOR signaling and increased AMPK pathway activation.	[123]
MCF-7	Triptolide	Increase	*In vitro*	The increase in rates of apoptosis and autophagy were the result of ERK activation.	[124]
MCF7	MicroRNA-26b	Inhibit	*In vitro*	The inhibition in apoptosis was mediated via targeting damage-regulated autophagy modulator 1	[125]
MCF-7	Licochalcone A	Increase	*In vitro*	Apoptosis was promoted by inhibiting the PI3K/Akt/mTOR pathway	[126]
MDA-MB-231	F1012-2 (Sesquiterpene lactones	Increase	*In vitro*	This agent decreased the expresion of cyclin B1, cdc2 and increased that of p21, p-cdc2, leading to apoptosis and autophagy	[127]
MCF7	Halilectin-3	Increase	*In vitro*	Halilectin-3 induced apoptosis via the caspase-9 pathway and induces autophagy by the expression of LC3-II	[128]
MDA-MB-231 and MDA-MB-468	Cantharidin	Inhibition	*In vitro* and *in vivo*	Cantharidin inhibited the advancement of TNBC by inhibiting autophagy and inducing apoptosis	[129]
MCF-7 and MDA-MB-231	Ursolic acid	Increase	*In vitro*	Ursolic acid downregulated PI3K and Nf-Kb signaling resulting in increased apoptosis and autophagy	[130]
MDA-MB-231	Glycyrrhizic acid	Increase	*In vitro*	Induction of autophagy was accompanied an increase in translocation of apoptosis-inducing factor to the nucleus.	[131]
MCF-7 and MDA-MB-231	Withaferin A	Inhibition	*In vitro*	This agent initially increased the substrates of autophagy but inhibited tubulin polymerization leading to impaired apoptosis.	[132]
MCF-7 and MDA-MB-231	Salinomycin	Increase	*In vitro*	Induction of apoptosis and autophagy was mediated by the effects of reactive oxygen species.	[133]
MCF-7 and MDA-MB-231	Cepharanthine	Increase	*in vitro*	This agent caused cell arrest in G0, apoptosis and autophagy in cancer cells.	[134]
MDA-MB-231, MCF-7, SK-BR-3	Ursolic acid	Increase	*In vitro*	By effecting the glycolysis pathway, Ursolic acid was able to induce cytotoxic autophagy.	[135]
MCF-7 and MDA-MB-231	Paris saponin	Increase	*In vitro*	This agent was able to induce autophagy via effecting the Akt-mTOR signaling cascade	[136]
MCF-7 and MDA-MB-231	2-ethyl-3-O-sulpamoyl-estra-1,3,5 (10),15-tetraen-17-ol	Increase	*In vitro*	Inducing autophagy resulted in cytotoxicity.	[137]
MDA-MB-231, MCF-7, SK-BR-3	Diosmin	Increase	*In vitro*	Diosmin increased p53, p21 and p27 levels and resulted in apoptosis, cell arrest and autophagy	[138]
MCF-7	paratocarpin E	Increase	*In vitro*	paratocarpin E promoted the nuclear transformation of NF-κB to the nucleus, promoting JNK signaling and inhibiting Erk signaling.	[139]
MCF-7	Ivermectin	Increase	*In vitro*	The increase in autophagy was mediated by inhibiting the signaling of the PAK1/Akt Axis.	[140]
MCF-7	Psoralidin	Increase	*In vitro*	This agent was able to burden cells with DNA damage which resulted in increased levels of DDR mediators and sensors, causing protective autophagy.	[141]
T-47D	14-Deoxy-11,12-didehydroandrographolide	Increase	*In vitro*	The GADD45A/p38 MAPK/DDIT3 pathway is involved in ER stress mediated autophagy.	[142]
MCF-7	Pseudolaric acid B	Increase	*In vitro*	This agent limited the interaction between BCL-2 and Beclin-1, thus promoting the role of Beclin-1 in the induction of apoptosis.	[143]

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Table 1 (*continued*)

Cell line	Agents Used	Effect on autophagy	Type of study	Results	Ref
MDA-MB-134 and MCF7	PD166866, (a FGFR1-selective inhibitor)	Increase	*In vitro*	This agent caused apoptosis by repressing the Akt/mTOR signaling	[144]
MDA-MB-231	Kallistatin	Increase	*In vitro*	This agent led to increase apoptosis and autophagy by effecting the signaling of Wnt/PPARγ pathway.	[145]
MDA-MB-231 and MCF-7	CYT-Rx20	Increase	*In vitro*	The MEK/ERK pathway was involved in inducing autophagy.	[146]
MCF-7 and MDA-MB-231	1,2,3-triazole analogs	Increase	*In vivo* and *in vitro*	Generation of reactive oxygen species induced autophagy and autophagy dependent apoptosis.	[147]
MCF-7 and MDA-MB-231	oleanolic acid (SZC017)	Increase	*In vitro*	This agent suppressed the levels of p65 and Akt and induced apoptosis.	[148]
MCF-7	Cucurbitacin B	Increase	*In vitro*	Induction of DNA damage by ROS led to increase in apoptosis	[149]
MCF7	Silibinin	Increase	*In vitro*	Silibinin induced apoptosis by mitochondrial dysfunction and loss of BNIP3	[150]
MCF-7 and MDA-MB-231	γ-Tocotrienol	Increase	*In vitro*	An increase in p38 and JNK1/2 signaling and a decrease in Erk1/2 signaling was coupled with an increase in autophagy and cell death.	[151]
SK-BR-3, MDA-MB-231, MCF7	YM155	Increase	*In vitro*	The pro-autophagic effects of this agent were in part mediated by inhibiting survivin.	[152]
MDA-MB-436 and MDA-MB-231	Oridonin phosphate	Increase	*In vitro*	Autophagy led to apoptosis in cancer cells	[153]
MDA-MB-231 and MCF-7	Ampelopsin	Increase	*In vitro*	Autophagy protected cancer cells form apoptosis.	[154]
HP-LTLC	VN/14-1	Increase	*In vitro* and *in vivo*	This agent showed excellent oral bioavailability in rats and successfully induced autophagy	[155]
MDA-MB-231	Lactaptin	Increase	*In vitro*	This agent caused cell death and autophagy which was independent of p53	[156]
MCF-7	Genistein	Increase	*In vitro*	This agent increased the ratio of BAX/Bcl-2, signaling the induction of apoptosis.	[157]
MCF-7 and MDA-MB-231	Artesunate	Increase	*In vitro*	Autophagy resulted in the induction of G2/M cell cycle arrest.	[158]
MDA-MB-231	HIMOXOL (oleanolic acid derivative)	Increase	*In vitro*	Autophagy was induced resulting from increased Beclin-1 and LC3-II expression	[159]
MCF-7	docosahexaenoic acid and eicosapentaenoic acid	Increase	*In vitro*	These agents increased the expression of PPARγ thus leading to inhibited AKT-mTOR signaling.	[160]
Bcap-37 and MCF-7	Pterostilbene	Increase	*In vitro*	By effecting the PI3K signaling, this agent had multiple anti-cancer effects.	[161]
MDA-MB-231	3-Methyladenine	Inhibit	*In vitro* and *in vivo*	By inhibiting autophagy, sensitivity to gefitinib was increased.	[162]
MDA-MB-231	Eriocalyxin B	Increase	*In vivo*	This agent was able to exert anti-tumor effects by inhibiting the Akt/mTOR/p70S6K signaling pathway.	[163]
MCF7, MDA-MB-231, T47D, MDA-MB-468	ADIPOQ/adiponectin	Increase	*In vitro*	Activation of ULK1 was resulted from a previous positive stimulation of STK11/LKB1	[164]
MDA-MB-231	Ethanol extract of propolis	Increase	*In vitro*	Anti-proliferative effects were seen by targeting the TLR4 signal cascade	[165]
MCF-7 and MDA-MB-231	Resistin	Increase	*In vitro*	Autophagy induced by Resistin caused resistance to doxorubicin induced apoptosis	[166]
MDA-MB-231, MDA-MB-453, MDA-MB-468 and MCF7	Jatamanvaltrate P	Increase	*In vitro* and *in vivo*	Expression of Cyclin B1, Cyclin D1 and Cdc-2 were decreased coupled with enhanced cleavage of PARP	[167]
MCF-7, SKBR3, MDA-MB-231, BT474	Juglanin	Increase	*In vitro*	Anti-cancer effects were mediated mainly via th ROS/JNK pathway	[168]
MCF-7	ZSTK474 (class I phosphatidylinositol 3-kinase inhibitor)	Increase	*In vitro*	Autophagy and cellular arrest in G1 are induced via blockade of PI3K/Akt/GSK-3β	[169]
MDA-MB-231	Curcumin	Increase	*In vitro*	Autophagy dependent AKT degradation caused a suppression of cellular migration and proliferation	[170]
MCF-7	SZC015 (oleanolic acid)	Increase	*In vitro*	PI3K/Akt/mTOR/NF-κB was inhibited leading to increased apoptosis and autophagy	[171]
T47D, Au565 and SUM149PT	Fluoxetine	Increase	*In vitro*	Anti cancer effects of this agent were mainly because of its ability to effect the endoplasmic reticulum and causing cell stress	[172]
MCF-7	fisetin	Inhibit	*In vitro*	This agent increased apoptosis via the activation of caspase 7, and inhibited autophagy	[173]
MDA-MD-231 and MCF7	Plumbagin	Increase	*In vitro*	Cell arrest and autophagy were achieved by blocking AKT/mTOR signaling	[174]
MCF-7	Apogossypolone	Increase	In vitro and *in vivo*	This agent mediated it anti cancer effects by targeting BCL-2, resulting in increased apoptosis and autophagy	[175]
SkBr3 and MDA-MB 231	Nexrutine	Increase	In vitro	This agent decreased the activity of (COX)-2 and PPARγ and the expression of cyclin D1 and CDK2. This agent caused apoptosis in SkBr3 and autophagy in MDA-MB 231	[176]
T-47D	Acetazolamide	Increase	In vitro	The expression of molecules such as ATG5, p53 and DRAM were increased.	[177]
MCF-7	Papuamine	Increase	In vitro	Autophagy is mediated via JNK signaling and damage to the mitochondria.	[178]
MDA-MB-231	Cucurbitane Triterpenoid	Increase	In vitro		[179]

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Table 1 (*continued*)

Cell line	Agents Used	Effect on autophagy	Type of study	Results	Ref
				Activation of PPAR γ is the upstream event resulting in apoptosis.	
MCF-7	RY10-4 (protoapigenone)	Increase	In vitro	Akt/mTOR suppression was accompanied with increased autophagy	[180]
MCF7 and MDA-MB-231	rapamycin and resveratrol	Inhibition	In vitro	Inhibition of autophagy led to increased apoptosis	[181]
MDA-MB-231 and MDA-MB-435	3-BrPA (Hexokinase II inhibitor)	Increase	In vitro	Autophagy was stimulated by an increased ROS production	[182]
Human breast cancer stem cells CD44(+)/CD24(−/low)	Rottlerin	Increase	In vitro	An increase in the expresion of LC3, Beclin-1 and Atg12 was witnessed which was followed by a decrease in the amounts of Bcl-2, Bcl-XL, XIAP and cIAP-1	[183]
MCF-7	Cyclovirobuxine D	Increase	In vitro	This agent increase the expression of markers of autophagy by inhibiting the Akt/mTOR signaling	[184]
MCF-7 and SUM159	Resveratrol	Increase	In vitro	Suppression of Wnt-b catenin signaling was followed by an increase in autophagy	[185]
MDA-MB-231 and MCF-7	G226 (epipolythiodioxopiperazine derivative)	Increase	In vitro	caspase-8 and caspase-3/7 activation was increased	[186]
MCF-7	Polygonatum odoratum lectin	Increase	In vitro	Apoptosis and autophagy were induced by inhibiting the EGFR-mediated Ras-Raf-MEK-ERK signaling	[187]
MDA-MB-231	Phellinus linteus extract	Increase	In vitro	This extract combined with 5-FU was successful in inhibiting the growth of cancer cells.	[188]
MCF7 and MDA-MB-231	alisertib (MLN8237)	Increase	In vitro	The pro-apoptotic and pro-autophagic response was mediated via effecting the p38 MAPK and Akt/mTOR signaling	[189]
HCC-1937, MDA-MB-436, SUM-149PT and HCC-1428	AZD2281 (Olaparib)	Increase	In vitro	This agent was able to induce autophagy and mitophagy in both BRCA1 and 2 mutated cancer cells.	[190]
MDA-MB231, Cal51 and MCF-7	YM155	Increase	In vitro	This agent cause cell death by autophagy and effecting the NF-KB signaling, which was not dependent on p53 signaling.	[191]
MDA-MB-231	SLC9A3R1	Increase	In vitro	This agent increased autophagy by effecting the PTEN-PI3K-AKT1 axis and stabilizing BECN1	[192]
MCF7	HIMOXOL	increase	In vitro	The pro-autophagic effects were mediated by effecting the ERK1/2 MAPK signaling	[193]
SKBr3 and MDA-MB-231	siramesine and lapatinib	Increase	In vitro	Treatment with these agents was also able to induce ferroptosis.	[194]
MCF-7	Hirsutanol A	Increase	In vitro	Autophagy was initiated by the accumulation of ROS.	[195]
MCF-7	MHY218	increase	In vitro	Induction of autophagy was able to induce cell death in chemo-resistant breast cancer cell.	[196]

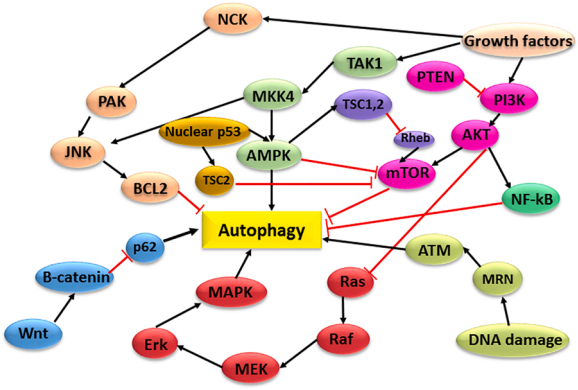

Fig. 1. The interplay between autophagy and DNA damage response mechanisms.

by Antonelli et al. has shown that there is a significant relation between the expression of ATM and autophagy related 4C cysteine peptidase (ATG4C). It is shown that breast cancer cells with the properties of cancer stem cells rely on the expression of both of these molecules to survive. The combined action of ATM and ATG4c promotes apoptosis in these cells [117]. Cell cycle progression has also important effects on autophagy. The key molecule in this regard is p53. This molecule can transactivate multiple key molecules involved in autophagy including AMPKβ1 and β2, Sestrin 1 and 2, tuberous sclerosis 2, PTEN and damage-inducible transcript 4(Ddit 4). Further, cytosolic p53 can inhibit autophagy [118]. This interaction has been studied as a target in breast cancer. MHY2256 (a SIRTs inhibitor) is able to induce autophagic death in MCF-7 cells by affecting the binding of MDM2-p53. Autophagy increment is recorded by the upregulation in LC3-II [119].

7. Conclusion

According to this review study, DNA damage response and various aberrations in its process could be both a starting point and a secondary happening in breast cancer. Likewise, apoptosis is also an important process in the pathogenesis of breast cancer both as a cancer promoting and protective factor. It is discussed that these two processes have potential to be targeted by various agents acting specifically on one of these functions or both of them to reduce cancerous cell emergence, inhibit proliferation and migration and metastasis, increase sensitivity to chemotherapy agents and radiotherapy, changes in tumor microenvironment, alterations in angiogenesis and more uncovered functions. Even more beneficence can be emerged by targeting signaling pathways which are interconnected with autophagy and DNA damage response namely PI3K signaling. Further, it is shown that cellular functions such as DNA repair, autophagy, cell cycle arrest and senescence are related to autophagy, then autophagy could have regulatory effects on these functions and could be a determining factor to target them. Noteworthy, many studies have been performed in targeting the interactions of autophagy and DDR and the aforementioned functions are still in early stages of clinical trials *in vivo* or *in vitro* studies. The ultimate result of these researches will direct future initiatives in targeting DDR and autophagy while constructing a new paradigm in targeted therapy of breast cancer.

Ethical approval

This article does not contain any studies with human participants.

Data availability statement

Research data not shared

Consent for publication

All authors have read the manuscript and approved the final version.

Funding

NO

Author contributions

Mohammad Mirza-Aghazadeh-Attari, Saber Ghazizadeh Darband and Mojtaba Kaviani participated in writing article. Ainaz Mihanfar and Forough Alemi participated in the data collecting. Shirin Sadighparvar, Simin Younesi, and Ansar Karimian Were involved in draw figure. Amin Safa roles were editing language. BahmanYousefi and Maryam Majidini aparticipated in the study design, manuscript drafting and revising.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Acknowledgments

The authors would like to thank Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Sciences for kind supports.

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