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REVIEW

The expression of galectin-3 in breast cancer and its association with chemoresistance: a systematic review of the literature

Ioannis Boutas[1,2] · Anastasios Potiris[1] · Walburgis Brenner[2] · Antje Lebrecht[2] · Annette Hasenburg[2] · Sophia Kalantaridou[1] · Marcus Schmidt[2]

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Abstract

Purpose Galectin-3 is a M_r 31,000 protein that belongs to a family of carbohydrate-binding proteins. Galectin-3 has already been associated with protection against apoptosis through cell to cell or cell to matrix adhesion processes. It seems that galectin-3 plays an important role in tumor progression, cell growth, invasion and metastasis. Galectin-3 is the only member of the chimeric galectins that has an N-terminal glycine and proline domain and a C-terminal carbohydrate recognition domain that allows galectin-3 to accommodate larger structures such us polylactosaminoglycans and intervene to DNA damage repair process. In this systematic review, our primary goal is to identify the effect of galectin-3 expression in association with drug resistance and apoptosis inhibition in breast cancer.

Materials and methods Scopus and PubMed databases were searched on 26 November 2018 using the following combination of keywords: (galectin-3 OR gal-3 OR LGALS3) AND (breast cancer) AND (chemoresistance OR (drug resistance) OR chemosensitivity). All the articles in English, regardless the time of publication, text availability and species included were initially accepted.

Results In the majority of the included studies, the expression of galectin-3 had a protective role in cell survival via different pathways such as the response to DNA damage and repair or the inhibition of apoptosis after treatment with a chemotherapeutic agent.

Conclusion Galectin-3 expression in breast tumors might be an important factor in the selection of the most suitable treatment.

Keywords Galectin-3 · Breast cancer · Chemoresistance · Chemosensitivity · Drug-induced apoptosis

Introduction

Galectin-3 is a M_r 31,000 protein that belongs to a family of carbohydrate-binding proteins which have affinity for b-galactoside containing glycoconjugates and conserved amino acid sequences in their carbohydrate-binding domains [1, 2]. It seems that galectin-3 plays an important role in tumor progression, cell growth, invasion and metastasis [3, 4]. Galectin-3 has already been associated with protection against apoptosis through cell to cell or cell to matrix adhesion processes. This is mediated by the recognition of cell surface glycoconjugates and by activating human neutrophils, pre-mRNA splicing and raising interleukin-1 levels by human monocytes [4–7]. Another important aspect is that galectin-3 is involved in tumor progression and apoptosis is by affecting the DNA damage repair response. DNA damage repair is a sophisticated process that includes injury detection and repair [8]. In that context, galectin-3 is the only member of the chimeric galectins that has an N-terminal glycine and proline domain and a C-terminal carbohydrate recognition domain that allows galectin-3 to accommodate larger structures such us polylactosaminoglycans and intervene to DNA damage repair process [9, 10]. By now, clinical research studies have correlated galectin-3 expression with several types of malignancies in head and neck, thyroid gland, gastric organs, colon and breast [11–15].

✉ Anastasios Potiris
apotiris@med.uoa.gr

[1] Third Department of Obstetrics and Gynecology, Attikon University Hospital, Medical School of the National and Kapodistrian University of Athens, Athens, Greece

[2] Department of Obstetrics and Women's Health, University Medical Center, Johannes Gutenberg-University, Mainz, Germany

Breast cancer is worldwide leading cancer in incidence and mortality for women [16]. In several studies, galectin-3 expression has been associated with breast cancer progression and metastasis using human breast cancer cell lines [17, 18]. Galectin-3 is the only known galectin with the capability to inhibit apoptosis [4]. This ability is a combined result of increased expression of anti-apoptotic proteins such us members of the Bcl-2 family and the ability to heterodimerize with Bcl-2 [5, 18–20]. Moreover, overexpression of galectin-3 has a protective impact on human breast cancer cells against tumor necrosis factor-α-induced apoptosis and nitric oxide-induced apoptosis [21]. Furthermore, it has been shown that galectin-3 levels are significantly higher in triple-negative breast carcinomas compared to non-triple-negative [22]. Ultimately, it has already been described that chemoresistance has been altered in galectin-3-silenced cancer cells [23].

Purpose of the review

In this systematic review, our primary goal is to identify the effect of galectin-3 expression in association with drug resistance and apoptosis inhibition.

Materials and methods

Scopus and PubMed databases were searched on February 26th, 2019 using the following combination of keywords: (galectin-3 OR gal-3 OR LGALS3) AND (breast cancer) AND (chemoresistance OR (drug resistance) OR chemosensitivity). All the articles in English, regardless the time of publication, text availability and species included were initially accepted. Through the initial research, 55 publications were retrieved.

Title and abstract of all 55 publications were screened independently by two reviewers (I.B. and A.P.) and the full text of the eligible ones was screened subsequently. If there was a study selected only by one reviewer, the decision was taken by a third reviewer (S.K.).

Only original studies were selected that included data about the specimen (rats, mice and human cell lines), the levels of galectin-3 and the use of a chemotherapeutic drug. Reviews, editorials, letters to the editor and studies with no drug tested or different cancer types were excluded from the study.

From the initial 55 records identified, 11 duplicates were removed leading to 44 studies at initial screening. After the initial screening, 20 studies were excluded because they did not confront with the inclusion criteria of the present review and 24 studies were selected for full-text assessment. Through the full-text assessment, one study was an editorial, seven was reviews of galectin-3 in all cancers, one was referred to colorectal cancer, one to gastric cancer, one in galectin-7 and its association with galectin-3 and in eight, there was no chemotherapeutic drug use. After the comprehensive evaluation, five studies were selected for data extraction as Fig. 1 shows.

Data extraction was completed by the one reviewer (A.P.) and cross-checked by the second reviewer (I.B.). Data that were extracted was: author, year of publication, institution, specimen and chemotherapeutic drugs used. Concerning the

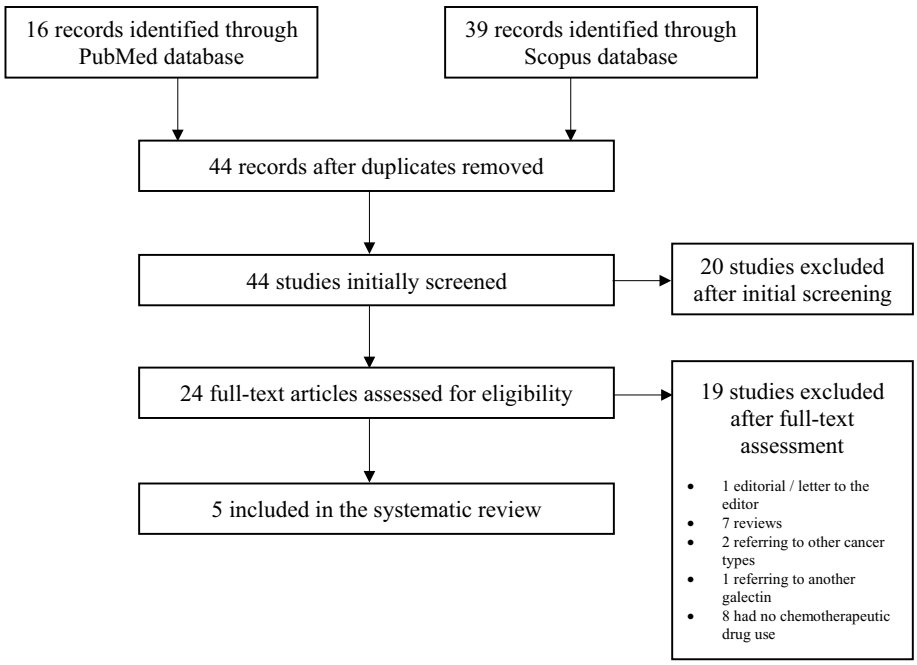

Fig. 1 Flow of the different phases of the systematic review

outcomes of each study, data about viability (time-dependent or not), apoptosis (time-dependent or not) and other associated protein levels were also extracted.

Results

cis-Diamminedichloroplatinum (CDDP)

Akahani et al. tested the significance of galectin-3 expression in cis-diamminedichloroplatinum cytotoxicity using sense and antisense (control) transfected, parental galectin-3-negative human breast carcinoma BT549 cell clones with confirmed and silence galectin-3 expression. After a 72-h exposure of 25 μm of CDDP, the viability of galectin-3-expressing clones was more than 60%, whereas in the silenced cell clones, was less than 30% [6]. Furthermore, to assess the apoptosis in the same CDDP-treated cells, they concluded that the apoptotic cells in the galectin-3 silenced clones were more than 30% in contrary to less than 20% of galectin-3-expressing clones. To further assess the morphologic features of apoptosis in the galectin-3-silenced population, more than 40% of the cells had morphologic features indicating apoptosis (DNA fragmentation and condensed chromatin), whereas the galectin-3-expressing cells had more visible nuclei without chromatin alterations [6]. With all the aforementioned facts, galectin-3 expression increases the chemoresistance of human breast carcinoma BT549 cell clones to CDDP and decreases the apoptotic effects of CDDP.

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

Mazurek et al. studied the effects of His64/Pro64 polymorphism of galectin-3 on its sensitivity to TRAIL. Nine breast cancer cell lines were analyzed concerning the sensitivity for TRAIL. After 4 h of treatment with 100 ng/mL of TRAIL, all the homozygous Pro64 galectin-3 cell lines were found not to be sensitive to TRAIL but all the homozygous His64 and one heterozygous were sensitive. Furthermore, they used BT549 cells for creating homozygous Pro64, homozygous His64 and heterozygous cell clones and found that TRAIL chemoresistance is significantly associated ($P < 0.05$) with Pro64 genotype [24]. Furthermore, when they tested galectin-3 null cell lines, after treatment with TRAIL, they found that they were also resistant to TRAIL [24].

Doxorubicin

In the previously described study, the authors additionally examined the doxorubicin sensitivity of BT549 cells with different polymorphism status after 16 h of treatment with 5 μg/mL of doxorubicin. Among the different genotypes, the sensitivity of doxorubicin was not found to alter. Moreover, the expression of His64 galectin-3 tends to render the cell lines more resistant to doxorubicin, whereas Pro64 galectin-3 has no effect [24].

Arsenic trioxide (ATO)

Zhang et al. used galectin-3-expressing MDA-MB-231 and MCF-7 breast cancer cell lines and showed that galectin-3 expression was significantly upregulated after 72 h of treatment with 2.5 mM of arsenic trioxide ($P < 0.01$) [25]. Regardless the higher levels of galectin-3, both cell lines showed a weak ATO-induced apoptosis. On the contrary, the galectin-3-knockdown MDA-MB-231 cell line showed a more than 20-fold increased apoptosis compared to control and a further two-fold increase when treated with ATO, suggesting that galectin-3 knockdown sensitizes these cells to ATO-induced apoptosis [25].

Etoposide, carboplatin and mitomycin C

Using silenced HEK293FT cell lines, Carvalho et al. performed cell viability assays after etoposide, carboplatin and mitomycin C treatment. Cells lacking galectin-3 expression showed an increased resistance to all three chemotherapeutic agents evaluated in all tested concentrations [26]. It is notable that *galectin-3*-silenced cells showed up to a 60% increase in viability when compared to control cells after treatment with 20 nM etoposide, suggesting that *galectin-3* has a major role in the cellular response to DNA damage and repair [26].

N-(4-Hydroxyphenyl)retinamide (4HPR)

Choi et al. tested the effects of 4HPR regarding viability and apoptosis on parental galectin-3-negative BT549 breast cancer cell clones. The three cell clones were a galectin-3-expressing line (BT549Gal-3Wt), an inactive galectin-3-expressing line (BT549Gal-3Mu) and an empty vector transfected, silenced galectin-3 line (BT549Vec). After a 3-day treatment with 5 μM of 4HPR, the inactive and silenced cell lines showed a marked reduction in survival. Namely, these cell lines had a 70–80% reduction in cell population whereas the reduction in galectin-3-expressing cell clones was about 25%, implying an association between galectin-3 expression and chemoresistance to 4HPR [27]. By assessing the apoptotic status of these cell lines with DNA fragmentation assays, they showed that after 2 days of treatment, about 40% of the cells were apoptotic in the inactive galectin-3 cell line and also apoptosis was observed in the galectin-3-negative group, whereas the galectin-3-expressing group was resistant to 4HPR even after 4 days of treatment [27] (Table 1).

Table 1 Results

Study	Year	Institution	Specimen	Drug	Outcomes in sensitivity and resistance
Shiro Akahani et al. [6]	1997	Wayne State University School of Medicine, Detroit, Michigan	Transfected human breast cancer cell line BT549	cis-Diamminedichloroplatinum (CDDP)	Galectin-3-expressing cell clones have increased viability after 72-h exposure to CDDP Galectin-3 inhibits apoptosis after 72-h exposure to CDDP Galectin-3-null and -positive cell clones showed no difference in the level of Bcl-2, Bcl-X_L and Bax protein expressions
Nachman Mazurek et al. [24]	2011	The University of Texas MD Anderson Cancer Center, Houston, Texas	Transfected human breast cancer cell line BT549 (Pro64His polymorphism)	Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and doxorubicin	TRAIL resistance is associated with the homozygous Pro64 genotype ($P < 0.05$) Sensitivity to doxorubicin is not dependent on galectin-3 genotype
Hao Zhang et al. [25]	2014	Department of Breast Surgery, the Second Hospital of Dalian Medical University, Dalian, China,	Human breast cancer cell line MDA-MB-231 and MCF7	Arsenic trioxide (ATO)	Galectin-3 expression significantly increased in MDA-MB-231 cell lines after treatment with ATO ($P < 0.01$) Galectin-3 knockdown in MDA-MB-231 cell lines increases apoptosis compared to control ($P < 0.05$) Galectin-3 inhibition sensitizes MDA-MB-231 cell lines to ATO-induced apoptosis
Renato Carvalho et al. [26]	2014	Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Brazil	Human HEK293FT cell line shGAL3: silenced gal3 cell lines shSCRB: control scramble sequence cell lines	Etoposide, carboplatin, mitomycin C	shGAL3 cells had statistically significant increase in viability when treated with etoposide or carboplatin or mitomycin c in all tested concentrations shGAL3 cells showed up to a 60% increase in viability comparing to controls after treatment with 20 nM of etoposide

Table 1 (continued)

Study	Year	Institution	Specimen	Drug	Outcomes in sensitivity and resistance
Jin-Hyuk Choi et al. [27]	2004	Department of Thoracic/Head and Neck Medical Oncology; The University of Texas M.D. Anderson Cancer Center, Houston, Texas USA	Human breast cancer cell line BT549 BT549Vec: neomycin-resistant control vector BT549Gal-3Mu: BT549 cells expressing mutant galectin-3 BT549Gal-3Wt: BT549 cells expressing wild-type human galectin-3	N-(4-Hydroxyphenyl)retinamide (4HPR)	5 μM of 4HPR after 24 to 72 h is leading to a time-dependent decrease in survival (70–80% reduction) of controls and those expressing inactive galectin-3. In contrast, cell lines expressing active galectin-3 showed only 25% reduction assuming that galectin-3 was conferring resistance to 4HPR In both BT549Vec and BT549Gal-3Mu, apoptotic cells comprised most of dead cells. On the other hand, most BT549Gal-3Wt cells were viable Both BT549Vec and BT549Gal-3Mu showed a four-fold increase of Intracellular ROS after the first 6 h of exposure to 4HPR. The later applies not to BT549Gal-3Wt cells After a 24-h exposure to 4HPR in both BT549Vec and BT549Gal-3Mu cell lines the levels of Cytochrome c increased implying mitochondrial apoptosis. In BT549Gal-3Wt cell lines 4HPR cytochrome c levels were stable 4HPR treatment led to decreased level of procaspase-3 or PARP cleavage in the control and mutant galectin-3 cell lines whereas in BT549Gal-3Wt cell lines the levels of both proteins remain unchanged

Discussion

cis-Diamminedichloroplatinum (CDDP)

Shiro Akahani et al. showed that galectin-3 expression increases the chemoresistance of human breast carcinoma BT549 cell clones to CDDP and decreases the apoptotic effects of CDDP. The authors concluded that galectin-3 inhibits apoptosis via a cysteine protease pathway and its affinity to BH1 domain of the Bcl-2 protein family [6]. The same results are observed through inhibition of galectin-3 in breast cancer cell lines as well as clear cell ovarian carcinoma and prostate cancer [28, 29].

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

The results of Mazurek et al. are in line with their previously published study showing that expression of galectin-3 in breast cancer cell lines alters sensitivity to TRAIL [30]. Since TRAIL transmits death signals, through death domain-containing receptors, it contributes to apoptosis but also against tumor growth and metastasis [31–33]. On their previous hypothesis, the alteration on TRAIL sensitivity is via upregulation of phosphatase and tensin analog (PTEN) which inactivates the phosphatidylinositol 3-kinase/Akt survival pathway [30]. Based on recent results, the His64/Pro64 polymorphism may alter the galectin-3 apoptotic effects. Furthermore, the His64 genotype but not the Pro64 is associated with decreased sensitivity to cisplatin and doxorubicin [24, 31].

Arsenic trioxide (ATO)

Hao Zhang et al. showed that galectin-3 expression reduces the sensitivity of breast cancer cell lines to treatment with arsenic trioxide and subsequently galectin-3 inhibition sensitizes the same cell lines to ATO-induced apoptosis. Arsenic trioxide is an inorganic compound that can inhibit tumor growth and induce apoptosis in many cancers such us acute promyelocytic leukemia and breast [34, 35]. In this research study, the authors showed that galectin-3 was located in the cytoplasm and was significantly higher expressed in breast cancer cells compared to non-cancer cells. Furthermore, triple-negative breast cancer (TNBC) was expressing predominantly galectin-3 as compared to other subtypes. This finding is in line with other studies in the literature [22, 25]. ATO-induced apoptosis has been proven in many preclinical studies for brain, liver, prostate, renal and breast cancers [36, 37]. It is supported by Hao Zhang et al. that the mechanism of the apoptotic effects of ATO may include the generation of reactive oxygen species (ROS) based on multiple myeloma studies [38].

Etoposide, carboplatin and mitomycin C

Carvalho et al. showed that silenced galectin-3-expressing cells had an increased resistance and delayed DNA damage repair response when treated with either etoposide, carboplatin or mitomycin C suggesting that galectin-3 has a notable role in DNA damage repair [26]. The authors suggest that galectin-3 is participating in complexes with BARD1 and BRCA1 and that it might regulate the BRCA1/BARD1 heterodimer recruitment to DNA damage sites [26]. This finding is in line with other observations suggesting that DNA damage repair involves G_2/M cell cycle arrest allowing mitosis after DNA repair [39]. The same events have also been described in BRCA1-deficient cells [40]. It is noteworthy that in the majority of the studies, galectin-3 has been associated with its anti-apoptotic characteristics and its induced chemoresistance. However, it seems that galectin-3 has also pro-apoptotic functions similar to BARD1 [41, 42].

N-(4-Hydroxyphenyl)retinamide (4HPR)

In their study, Jin-Hyuk Choi et al. showed that galectin-3 is associated with increased viability and protection against apoptosis in cell lined treated with 4HPR. 4HPR is a synthetic retinoid which has a proven ability to induce apoptosis in a variety of cell lines with hematological cancers, neuroblastomas, prostate, bladder, head and neck and lung cancer [43–48]. Moreover, its beneficial act has been seen and evaluated in clinical studies for breast and ovarian cancer [49, 50]. To identify the cause of this reduction in apoptosis, they investigated different known apoptotic pathways. Regarding the intracellular reactive oxygen species (ROS), they found that 4HPR caused a linear increase of ROS compared to silenced and inactive galectin-3 cell lines. On the contrary, the galectin-3 expressing group only showed a rather small increase in ROS generation [27]. To further investigate whether galectin-3 expression is the cause of the decreased ROS-induced apoptosis, they treated all three cell lines with H_2O_2 and reached the conclusion that galectin-3 expression does not lead to resistance to ROS-induced apoptosis but alters the ability of 4HPR to increase ROS generation. The same impact of galectin-3 expression to ROS generation has been also described after treatment with TNFα [51].

Another pathway investigated by the same group was the Bcl-2 family protein expression which has a well-known association with apoptosis [19]. After treatment with 4HPR, there was a reduction in Bcl-2, Bcl-x_L and Bax in both active and inactive galectin-3-expressing groups. The impact of 4HPR in these proteins in the inactive galectin-3

cell lines was more pronounced than in the silenced lines and the appearance of Bax fragments was only noticed in the silenced group. Since the exact impact of 4HPR to these proteins is not yet identified, the authors suggested that ROS created by 4HPR lead to decreased Bcl-2 expression and Bax fragments. This hypothesis is also supported by other studies suggesting that ROS generation can directly modify the Bcl expression [20, 52, 53].

Finally, they also measured the levels of cytochrome c and activated caspase-3. Since the release of cytochrome c into the cytosol is a sign of mitochondrial apoptosis, they described that levels of cytochrome c increased after the first day of treatment with 4HPR in both silenced and inactive galectin-3 cell lines, whereas in galectin-3-expressing group, cytochrome c levels were not elevated [27, 54]. Regarding the activated caspase-3 levels, the authors found that in both inactive and silenced lines, a decrease in pro-caspase-3 indicates the production of activated caspase-3. In contrast, these results were not confirmed in the galectin-3-expressing group [27]

Conclusion

In the present review, we have listed the published data regarding galectin-3 expression and its association with chemosensitivity and chemoresistance in breast cancer. In the majority of the included studies, the expression of galectin-3 had a protective role in cell survival via different pathways such as the response to DNA damage and repair or the inhibition of apoptosis after treatment with a chemotherapeutic agent. Hence, galectin-3 expression in breast tumors might be an important factor in the selection of the most suitable treatment.

This is, to the best of our knowledge, that first study thoroughly reviewing the effects of galactin-3 to chemosensitivity and chemoresistance in breast cancer. Moreover, the potential clinical impact in treatment selection is considered a strength. The limitations of our review are the relatively small amount of studies included, the lack of clinical studies and the lack of published data for long-term treatment.

However, galectin-3 expression and its impact is a very interesting field for future studies. There are not any published studies thus far regarding the effects of galectin-3 in cell lines treated with taxanes, anthracyclines and cyclophosphamide. This is a potential field for future research.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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