CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
https://cajmns.casjournal.org/index.php/CAJMNS
Volume: 07 Issue: 03 | July 2026 ISSN: 2660-4159

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Article

The Emerging Role of Galectin-3 in Breast Cancer Progression, Metastasis, and Therapeutic Resistance: A Comprehensive Review

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Abstract: Breast cancer remains the most frequently diagnosed malignancy among women worldwide and is a leading cause of cancer-related mortality. Despite significant advances in early detection and treatment strategies, tumor progression, metastatic dissemination, and therapeutic resistance continue to pose major clinical challenges. Increasing evidence has identified galectin-3, a β-galactoside-binding lectin, as a multifunctional regulator involved in various aspects of breast cancer biology. This review aims to comprehensively summarize the emerging role of galectin-3 in breast cancer progression, metastasis, and resistance to therapy. Galectin-3 participates in multiple cellular processes, including cell proliferation, apoptosis evasion, angiogenesis, epithelial–mesenchymal transition, immune modulation, and extracellular matrix remodeling, all of which contribute to tumor growth and metastatic potential. Elevated galectin-3 expression has been associated with aggressive clinicopathological features, enhanced invasion, and poor patient outcomes in several breast cancer subtypes, particularly triple-negative breast cancer. Furthermore, galectin-3 influences tumor–microenvironment interactions by promoting immune escape mechanisms and facilitating communication between cancer cells and stromal components. Recent studies have also demonstrated that galectin-3 contributes to resistance against chemotherapy, targeted therapies, and immunotherapy through the activation of survival signaling pathways and the maintenance of cancer stem cell properties. In addition to its biological significance, galectin-3 has emerged as a promising diagnostic, prognostic, and predictive biomarker with potential utility in patient stratification and treatment monitoring. Therapeutic approaches targeting galectin-3, including small-molecule inhibitors, monoclonal antibodies, and combination treatment strategies, have shown encouraging preclinical results and may offer novel opportunities for improving clinical outcomes. Collectively, current evidence highlights galectin-3 as a pivotal mediator of breast cancer progression and treatment resistance, underscoring its potential as both a biomarker and a therapeutic target in precision oncology.

Keywords: Galectin-3; Breast Cancer; Metastasis; Therapeutic Resistance; Tumor Microenvironment.

Citation: Muner, Q, A, E & Hamad, A. H. The Emerging Role of Galectin-3 in Breast Cancer Progression, Metastasis, and Therapeutic Resistance: A Comprehensive Review. Central Asian Journal of Medical and Natural Science 2026, 7(3), 583-596

Received: 10th Mar 2026
Revised: 21th Apr 2026
Accepted: 08th May 2026
Published: 15th June 2026

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1. Introduction

Galectin-3 functions as a molecular mediator in breast cancer, integrating structure–function insights with evidence on initiation, progression, metastasis, and resistance to therapy; synthesize mechanisms, biomarkers, and translational potential with emphasis on current data and gaps [1].

Over three million women were diagnosed with breast cancer in 2020, making it the most frequent cancer. Breast cancer remains a major cause of cancer death among women, particularly for metastasis and therapy resistance. Galectins are defined by carbohydrate

recognition domains that bind β-galactosides, and galectin-3 is the only chimera-type member, with a unique structure, and an evolutionarily conserved function. Like many galectins, galectin-3 is upregulated in cancer, controlling multiple traits associated with malignancy. Evidence indicates that the galectin-3 gene is an oncogene in breast cancer, with its product acting as a molecular conductor of localized and systemic adaptations supporting disease initiation, progression, spread, and therapy resistance [2,3].

The galectin-3 protein and its gene are overexpressed in many types of breast cancer, being modulated by the main classes of therapeutic intervention. Preclinical studies have demonstrated that galectin-3 participates in tumor growth and plays a non-redundant role in breast cancer metastasis. Increasing evidence indicates that galectin-3 contributes to resistance to endocrine and chemotherapy, antibody therapy, and immunotherapy. A detailed understanding of the pleiotropic functions of galectin-3 in breast cancer is required to unveil its potential as a therapeutic target, biomarker, or route to overcome therapy resistance [4].

Galectin-3: Structure, Expression, and Functional Overview

Galectin-3 is a member of the galectin family of proteins, which mediate a wide range of biological processes, including cell-cell and cell-extracellular matrix interactions, regulation of signaling pathways, gene expression, and cell trafficking. In mammals, 15 galectins with different domain structures and arrangements have been characterized. Galectin-3 exhibits a unique protodomain a single carbohydrate recognition domain, C-terminal domain, and extended flexible hinge that interconnects these two domains. These features allow the protein to function as a homodimer and form higher-order oligomers [5,6]. Galectin-3 is secreted by various cells and accumulates in the extracellular space, where it exerts multiple biological functions by interacting with glycoproteins and glycolipids on the cell surface and in the extracellular matrix, modulating the activity of neighboring cells and affecting tumor progression. In addition, galectin-3 is present in cytoplasmic cytosol, cytoplasmic organelles, and nuclei of normal, damaged, and cancer cells. Within cells, galectin-3 participates in diverse cellular functions, including autophagy, apoptosis, and proliferation. It has also been implicated in obesity-associated metabolic disorders and tumor development and progression [7,8].

In breast cancer, galectin-3 has emerged as a multifactorial molecular switch that functions as both a promoter and suppressor in tumor initiation, progression, and metastasis, depending on the biological context. Increasing evidence indicates that it facilitates resistance to chemotherapy and other therapy modalities, including endocrine therapy, immunotherapy, and anticancer vaccines. Mechanistic pathways that link galectin-3 to the initiation and progression of breast cancer have started to be elucidated and include its multiple roles in regulating cell adhesion, signaling pathways, metabolism, and circulating tumor cells. These developments complement earlier data implicating galectin-3 in breast cancer progression and offer the prospect of developing galectin-3-based biomarkers and therapeutic strategies in breast cancer [9].

2. Materials and Methods

Design: A narrative literature review was performed to give an overall assessment of the new role for galectin-3 in breast cancer progression, metastasis and therapy resistance. Significant efforts were made to identify relevant scientific literature through extensive searches in some of the major biomedical databases, including PubMed, Scopus, Web of Science, Google Scholar and ScienceDirect. The search methodology utilized the Boolean operators to merge keywords including “Galectin-3,” “Breast Cancer,” “Metastasis,” “Therapeutic Resistance,” “Tumor Microenvironment” and combination with terms such as Key Phrases, "biomarker", "immunotherapy" and 'targeted therapy', in order to ensure all relevant studies would be retrieved. Emphasis on recently published, peer-reviewed literature (2014–2026) in the English language was applied given that more recent discoveries shedding light on known aspects of galectin-3 biology may not have been fully elucidated until this review was initiated. Key mechanistic or ground-breaking studies published prior to this time were also included, when deemed essential.

You screened titles, abstracts and full texts to identify studies that directly investigated biological, molecular, and clinical significance of galectin-3 in breast cancer. We included original experimental studies, clinical investigations, and systematic reviews and meta-analyses that assessed the relationship between galectin-3 expression with tumor initiation, proliferation, epithelial–mesenchymal transition (EMT), metastatic dissemination, immune evasion, therapeutic resistance and patient outcomes. The review excluded studies without adequate methodological rigor (i.e. low quality, out of scope based on clinical question or hypothesis to test) not measuring breast cancer, and those providing very little evidence concerning galectin-3 overall.

Qualitative synthesis of the selected studies were performed against major thematic domains; including–galectin-3 structure and function, mechanisms of tumor progression, metastatic pathways, resistance to endocrine therapy, chemotherapy/targeted therapy/immunotherapy (CTT), biomarkers and emerging CTT strategies. Findings were compared to using a comparative analysis technique and consistently found, contradicting evidence was noted and current gaps in research also identified. This integrated approach provided a holistic view of galectin-3 as a promiscuous modulator of breast cancer biology and illuminated its potential utility as an actionable tissue prognostic biomarker and therapeutic target for future precision oncology approaches.

3. Results and Discussion

Galectin-3 in Breast Cancer Initiation and Tumor Growth

Ongoing studies now suggest that galectin-3 also plays a pivotal role in the earliest events of breast cancer development and subsequent tumor growth. Recent evidence indicates that galectin-3 can regulate estrogen receptor differentiation and activity, thus influencing resistance to endocrine therapy. In the initial stages of tumor development, galectin-3 secretion from neoplastic cells facilitates their proliferation and augments the inflammatory infiltrate. At later stages, however, paracrine signaling from the tumor-associated stroma supports cancer survival, and tumor cells exploit the “danger-signal” feature of galectin-3 to promote an inflammatory environment supporting their growth. Analysis in transgenic mouse models indicates that galectin-3 may act both in a pro-inflammatory and pro-tumorigenic capacity [10,11].

Despite the general consensus that galectin-3 promotes breast cancer progression, several studies have explored its potential tumor-suppressor function during the early stages of neoplastic development. Research in transgenic mice produces conflicting results; some report that galectin-3 deficiency accelerates tumor growth, whereas others document a different effect characterized by reduced angiogenesis, inflammatory infiltration, and tumor-associated macrophage recruitment. Nevertheless, accumulation of myeloid-derived suppressor cells is consistent with the notion that galectin-3 contributes to tumor promotion. Further inquiry is warranted to clarify the role played by this lectin in distinct mouse models at different stages of tumor initiation and development. Breast cancer initiation has previously been linked to galactose metabolism; key enzymes of the Leloir pathway were identified as being downregulated during oncogenic transformation in breast epithelium [12,13].

Galectin-3 and Breast Cancer Metastasis

Breast cancer metastasis is responsible for about 90% of breast cancer mortality. The VTN–ITGB3 axis on CTCs plays an integral role in dissemination by diminishing adherence and promoting tumor-initiating capacity. Galectin-3, which promotes the shedding of mucins and CD44, increases the number of circulating tumor cells. Endometrial carcinoma cells shed extracellular vesicles containing galectin-3 that modify macrophages in the premetastatic niche enabling successful dissemination. Galectin-3 correlations with organ-specific tropism exist in breast-to-bone and melanoma-to-brain models. In triple-negative breast cancer, the nucleolin–galectin-3–EGFR pathway governs colonization of the premetastatic lung [14,15].

Galectin-3 and Epithelial-Mesenchymal Transition

Epithelial–mesenchymal transition (EMT), characterized by loss of epithelial features and acquisition of mesenchymal properties, facilitates dissemination of cancer cells from tumor sites [16,17]. Increasing evidence indicates that galectin-3 plays a central role in EMT induction during breast cancer progression. Multiple tumor-related stimuli—including transforming growth factor (TGF)-β, epidermal growth factor (EGF), and interleukin (IL)-6—and signaling pathways—including SMAD, phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase—induce galectin-3 expression. Increased levels of galectin-3 enhance migration, invasion, and stemness of breast cancer cells in vitro and promote metastasis to lungs and liver in vivo. Galectin-3 knockdown significantly diminishes the pro-EMT effects of TGF-β, EGF, and IL-6 on breast cancer cells 18. These findings underscore a pivotal role for galectin-3 in mediating EMT in breast cancer progression [18,19].

Galectin-3 and Circulating Tumor Cells

Breast cancer metastasis is a multi-step process, beginning with local invasion, followed by entry into the lymphatic and blood circulatory systems, dissemination to distant sites, and colonisation of secondary sites 22. Circulating tumor cells (CTCs) originate from primary tumors and travel throughout the organism, gaining access to blood and lymph vessels through opening breaches in the lymphatic and vascular endothelium 23. CTCs leave the circulation and settle at distant sites in a selective manner linked to organ-specific metastasis, targeting highly vascularized organs such as the lungs and liver before colonising less vascularised organs 18. Galectin-3 sustains the metastatic process by controlling the viability of CTCs, the number of cells shedding from the primary tumor, and the capacity of CTCs to adhere to, migrate through, and invade organs by regulating the expression of adhesion molecules at the plasma membrane [20,21]. The secretion of galectin-3 by tumor cells under lymphatic, vascular, and nutrient stress promotes the formation of CTC clusters and enables single cells to progress through dormancy, suggesting a fundamental role in assisting CTCs to survive in the bloodstream and ultimately foster metastatic colonization [22,23].

Galectin-3 in Organ-Specific Metastatic Tropism

Considerable evidence indicates that galectin-3 is involved in organ-specific metastatic tropism. At the bone marrow microenvironment stage of hematological cancers, galectin-3 expression is upregulated, enabling the ability of neoplastic cells to proliferate, migrate, and resist antitumor treatment 18. Experiments with galectin-3 knockout mice indicated that galectin-3 may also affect the bone marrow microenvironment by modulating skillfulness of hematopoietic cell differentiation through secretion regulation of GM-CSF. In mammary carcinoma models, galectin-3 promotes metastasis to the lung by enhancing circulating tumor-cell (CTC) dissemination and homing. Galectin-3–mediated CTC growth is dependent on the CTC epithelial-to-mesenchymal transition (EMT) status and the lung microenvironment response. Galectin-3 might facilitate adaptation of CTC to the lung microenvironment, enabling lung metastasis formation and the development of tools to examine these processes, including anticancer drug resistance, are necessary [24,25].

Galectin-3 and Therapeutic Resistance in Breast Cancer

Emerging data indicates a role for galectin-3 (Gal-3) in mediating resistance to diverse breast cancer therapies, including endocrine, cytotoxic, and antibody-based immune therapies. In endocrine-resistant models, Gal-3 supports survival and growth via mesenchymal-like features, while other sources identify Gal-3 as a key player in the protective response against HER2-targeted therapy. Moreover, Gal-3 overexpression in tumors correlates with decreased tumor-infiltrating lymphocytes and a propensity for immune evasion, highlighting a downstream function in resistance to immune checkpoint blockade. Whether Gal-3 plays a role in resistance to other therapeutic modalities particularly, chemotherapy remains to be fully defined [26,27].

Endocrine therapy resistance. Among therapeuic modalities, the evidence supporting a role for Gal-3 in endocrine therapy resistance is the most extensive. Resistance to estrogen deprivation is thought to arise from both intrinsic and extrinsic mechanisms that

enable tumor cell survival despite the absence of estrogen. Intrinsic mechanisms include an epithelial to mesenchymal transition (EMT)-like switch, enabling tumor cells to bypass the ERα-dependent reliance on estrogen for survival and growth [28,29]. Riemann et al. showed that constitutive expression of Gal-3 is sufficient to induce such a protective response, as ERα-deficient MCF-7 cells rendered Gal-3-positive by genetic manipulation expressed the EMT transcript program and were protected from estrogen deprivation. Moreover, they identified Gal-3 as a downstream transcriptional target of the lysophosphatidic acid receptor LPAR1, whose expression is itself upregulated in aromatase inhibitor-resistant tumors, thereby connecting LPAR1 signaling with the ability to survive estrogen deprivation in a Gal-3-dependent fashion. In utero, through the selection of metastatically competent cells and through the modulation of the TME, Gal-3 contributes to the emergence of tumors that are refractory to endocrine therapy [30,31].

In another endocrine-resistant model based on prolonged exposure to the selective ER modulator tamoxifen, Weyler and colleagues demonstrated that tumor cells activate a bicosanoid pathway that converts a blunted response to tamoxifen into a Gal-3-dependent proliferative signal. However, in this setting, instead of promoting Gal-3 expression, the bicosanoid pathway converged on the release of Gal-3 from tumor-infiltrating macrophages. Despite its origin, the pro-tumorigenic activity of Gal-3 remained conserved, and neutralization with an anti-Gal-3 antibody attenuated the growth of tamoxifen-resistant xenografts [32].

Endocrine Therapy Resistance

Breast tumors expressing hormone receptors frequently respond to endocrine therapies that inhibit hormonal signaling; however, such responses are typically transient. While the use of fulvestrant (an estrogen receptor antagonist) initially inhibited tumor growth and reduced circulating tumor cell levels, galectin-3 expression persisted and increased in residual tumors. Notably, within CTCs, high galectin-3 expression occurred in a subset of ER+ tumors predicted to be resistant to endocrine therapy. Galectin-3 may facilitate these effects by regulating ERα function and transcriptional activity in CTCs. Galectin-3 also mediates responses to endocrine therapy in ERα-positive breast cancer cells. Estradiol induces galectin-3 expression through the action of signal transducer and activator of transcription 3, and in turn, galectin-3 enhances the expression of estrogen-responsive genes, exacerbating the growth of ERα-positive tumors. Moreover, galectin-3 interacts with ERα and rescues ERα signaling following fulvestrant treatment by preventing ERα degradation, thus contributing to endocrine therapy resistance [33].

Galectin-3 undergoes polar overexpression and is secreted by cyclin D1-induced tumor-associated macrophages, promoting the translocation of ERα into the nucleus. Hence, galectin-3 secretion by macrophages surrounding ERα-positive breast cancer modulates cell proliferation and contributes to tumor progression through the regulation of ERα expression and activity in breast cancer cells. Notably, secretion of sLex-bearing mucin-1 by breast cancer cells enables endocrine therapy resistance through macrophage M2 polarization, and galectin-3-binding protein supports the therapeutic failure of tamoxifen through the promotion of epithelial–mesenchymal transition and immune escape [33,34].

Tamoxifen induces the levels of galectin-1 and galectin-3 in hormone receptor-positive breast cancer patients. In 64 patients, high serum levels of galectin-1 and/or galectin-3 were independently associated with poor disease-free survival. Following surgery and tamoxifen treatment of hormone receptor-positive breast cancer with or without HER2 amplification, serum galectin-3 levels were significantly decreased in patients with favorable prognostic indicators, whose disease was not clinically complicated by distant metastasis and/or residual lesions; however, these levels were restored in those with an overall poor prognosis. Thus, alterations and significance of galectin-3 in breast cancer may differ depending on patient characteristics, particularly those relevant to prognosis [34].

Chemotherapy and Targeted Therapy Resistance

In cancer, the acquisition of resistance to chemotherapy is a major contributor to treatment failure. Data from mouse models showed that high expression of galectin-3 in

breast tumors leads to intrinsic resistance to doxorubicin, with a mechanism involving the enhanced expression of ATP-binding cassette sub-family G member 2 (ABCG2). In breast cancer patients, high levels of galectin-3 mRNA in the tumor were associated with decreased progression-free survival following chemotherapy. In triple-negative breast cancer (TNBC), galectin-3 regulates cell response to paclitaxel and cisplatin. Overexpression of galectin-3 confers resistance to both drugs through upregulation of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2), while inhibition of galectin-3 reduces cell viability and enhances apoptosis. Moreover, galectin-3 contributes to paclitaxel resistance in the cytotoxic-resistant TNBC cell line HCC1806 by promoting cell migration, which correlates with increased expression of ABCG2 and phosphorylated p38 mitogen-activated protein kinase [35,36].

Evidence suggests that galectin-3 might also mediate resistance to trastuzumab in HER2-positive breast cancer. Exogenous galectin-3 enhances the ability of HER2 to promote cell cycle entry, whereas shRNA-mediated silencing of galectin-3 impedes the proliferative effects of the HER2 receptor in the presence of trastuzumab. However, additional studies involving primary tumors are needed to further clarify the potential role of galectin-3 in anti-HER2 therapy response [37].

Immunotherapy Resistance and Immune Evasion

Evidence suggests that galectin-3 contributes to resistance to immune checkpoint inhibitors, and that blockade of galectin-3 in combination with anti-PD-1 therapy re-sensitizes therapy-resistant murine models of breast cancer to T cell-mediated rejection. Galectin-3 can also promote potently immune-suppressive and protumorigenic tumor-associated macrophage polarization towards a CD206+ and CD64+ phenotype, associated with reduced IFN-γ production by CD4+ T cells and enrichment of Th17 subsets. The engagement of galectin-3 by apoptotic cells in the tumor microenvironment dampens the capacity of tumor-associated dendritic cells to activate T cell responses, subsequently inhibiting T cell proliferation and differentiation into effector cells. Hence, galectin-3 can play a multifactorial role in supporting breast cancer immune evasion, with effects on both innate and adaptive compartments [38,39].

High expression of Galectin-3, Galectin-9, and the cognate receptors Tim-3 and PD-1 has been detected in human breast tumors, and elevated levels of sGal-3 in serum correlate with CD3+ T cell infiltration and with worse prognosis. Increased galectin-3 expression favors immune evasion by promoting the recruitment of myeloid-derived suppressor cells in the tumor microenvironment, which upregulate immune-checkpoint molecules on CD8+ T cells or produce IL-10 to inhibit CD4+ T cell proliferation. The blockade of sGal-3 with the anti-galectin-3 antibody, ABBP-1, strongly inhibited breast tumor growth, and combined treatment with anti-PD-1 antibodies alleviated T cell anergy, suppressing tumor growth and metastasis. Galectin-3 expression levels have also been linked to response to PD-1 blockade in mouse melanoma models. In further support of a contribution of galectin-3 to immune evasion and therapy resistance, galectin-3 inhibition enhances the therapeutic efficacy of Bacillus Calmette-Guérin immunotherapy in a model of rat breast cancer [40].

Mechanistic Pathways Linking Galectin-3 to Breast Cancer Biology

Extensive evidence documents that the glycan-binding protein galectin-3 influences several mechanisms implicated in breast cancer. Cell adhesion and extracellular matrix interactions mediated by galectin-3 are extensively characterized. Emerging roles in metabolic reprogramming, control of extracellular vesicle content and function, and several signaling pathways activated by or affecting galectin-3 provide new opportunities for understanding galectin-3 biology [41]. Galectin-3 impacts breast cancer biology by controlling the expression of key players in metastasis, such as tenascin-C, TWIST1, and S100A4, in breast cancer cells or in the tumor microenvironment. Role in the immune landscape of breast cancer and response to immunotherapy is supported by recent, although still limited, evidence [42].

Breast cancer initiation, progression, and metastasis are associated with major modifications in the tumor microenvironment. Galectin-3 is emerging as a pivotal component of these modifications through its effects on extracellular matrix (ECM)

remodeling, on the composition and functionality of cancer-associated fibroblasts, and on the production of extracellular vesicles. The influence of the biological activity of tumor-expressed galectin-3 in orchestrating the molecular program associated with distant metastasis has possibly broader implications. In breast cancer models without invasive capacity, the ectopic expression of galectin-3 or of TWIST1 suffices to drive tenascin-C and S100A4 expression, supporting the notion that galectin-3 may prime selected breast cancer cells for metastasis [43].

Cell Adhesion and Extracellular Matrix Interactions

Disruptions in homeostatic expressions of galectin-3 are implicated in several stages of malignancy. Within the tumor microenvironment, galectin-3's engagement with various glycan structures of cell-surface molecules or molecules secreted into the extracellular matrix (ECM), its multimerization, and its ability to function as a bridge between different cellular partners may facilitate critical functions in tumor cells and tumor-associated stromal and immune cells [44].

Galectin-3 interacts with cell-surface glycoproteins involved in cell adhesion, including laminin, syndecans, mucins, galectin-3-binding protein, the leucine-rich repeating protein R3, and the L1 intercellular adhesion molecule. By binding to suicidal cell death receptors, galectin-3 may also negatively regulate their signaling. It binds also to IgA and IgM and affects B-cell receptor cross-linking, regulating B-cell activation and maturation. The sialic-acid-binding nature of galectin-3-Gal combination contributes to the adhesion of tumor cells to the endothelium. In addition, the ability of galectin-3 to recognize several glycoproteins expressed in a polarized manner by epithelial cells may enable it to play adhesive roles in the tropism of specific tumors [45].

High expression levels of galectin-3, both in glioma cells and in exosomal vesicles, are correlated with tumor malignancy and play a pivotal role in maintaining a malignant phenotypic state through interference with L1 cell adhesion molecule-mediated cell-cell junctions and modulation of β-catenin/Wnt signaling. The interaction between L1 and galectin-3 may also modulate cellular homeostasis and neuronal circuit assembly during development. In addition to functioning as a ligand for several receptors on different cell types (fibroblasts, monocytes, macrophages, etc.) and as a handle for closed cell-cell communication, galectin-3 also modulates the activity of growth factors and cytokines (PDGF, TGF-β1, LIF) [46].

Signaling Pathways Modulated by Galectin-3

In breast cancer progression, the integrated expression of galectin-3 and protein kinases has been shown to affect certain Wnt–β-catenin-dependent oncogenic pathways involved in cell proliferation and apoptosis. The Wnt glycoproteins are recognized modulators of post-embryonic development that often act through signaling pathways that have aberrant expression in malignancies. Moreover, β-catenin is known to be a central actor in promoting tumorogenesis in several cancer types, while galectin-3 is differentially expressed and secreted to enhance tumor-cell survival, migration, and invasiveness. In this setting, nuclear-galectin-3 expression was shown to be positively correlated with the nuclear localization of β-catenin, as well as with the nuclear and cytoplasmic expression of c-Myc and cyclin D1. Functionally, resumptive downregulation of galectin-3 expression in MDA-MB231 cells resulted in the attenuation of both β-catenin nuclear translocation and the consequent transcription of its target genes [47,48].

Moreover, galectin-3 cooperates with beta-catenin to enhance cell motility and invasiveness in inflammatory breast cancer. Galectin-3 depletion leads to a remarkable downregulation of the chemokine receptor CCR7 and the Wnt–β-catenin target VCAM-1 by impairing the transcriptional activity of β-catenin. Consistent with an EMT-driven metastasis model and with the observation that galectin-3 is critical for leukocyte recruitment in breast cancer, these data point to an essential role of CCR7 in IBTC cell migration and tumor spread. Furthermore, galectin-3 has been shown to be involved in the regulation of the NF-κB pathway in response to several inflammatory stimuli through distinct mechanisms in different cell types. Several studies provide evidence that galectin-3 is required for full NF-κB activation. Importantly, direct interaction between galectin-3 and IκB, the cytoplasmic inhibitor of NF-κB, facilitates NF-κB nuclear translocation by

promoting degradation of IκB. Recently, galectin-3 has also been proposed to mediate NF-κB activation triggered by palmitic acid [49,50].

Interplay with Extracellular Vesicles and Metabolic Regulation

Galectin-3 is expressed in all cell types; however, its activity can differ in various cell types depending on their microenvironment. Galectin-3-containing exosomes, for example, control immune response during breast cancer progression. Riemann et al. employ silenced tumor cells to demonstrate that Galectin-3 deficiency results in ejection of Galectin-3 from tumor cells. Loss of cardiac Galectin-3 causes early transcriptional upregulation of PPAR-γ and downregulation of SOCS-1 in grafted tumors, ultimately protecting these mice from metastases. Connecting tumor cells to their microenvironment preparatory for metastatic outgrowth are vascular changes involving EV-carried S100A4 and Galectin-3 supply and potential opening of the blood-brain barrier [51]. Exosomal Galectin-3 might induce distant-preconditioning in endothelial cells. In the metabolism context, Zhang et al. establish temporal homeostatic pH control over the conversion of the lactate courier MCT4 during bee venomic studies and found that lactate-MCT4-Gal-3-mediated signaling activates the NF-κB pathway and subsequently triggers MMP-2 elevation [52].

Fluorescence detection for Galectin-3 and its receptor-binding upstream protein MCT4, known to regulate lactate production and distribution, indirectly measures tumor acidity. Restoration of MCT4 or pH neutralization counteracts the bee venom–induced Galectin-3 elevation, and metabolomics confirms a link between lactate and Galectin-3; together with pharmacologic lactate targeting and overexpression studies. Integrated analysis thus reveals Galectin-3-MCT4–associated metabolic alteration as a bee venom–facilitated event underpinning the generation of nanomaterials for latent autoimmune diabetes in adults immunotherapy. These studies support models and treatment targeting based on the Galectin-3-associated transcription regulatory circuitry in diabetic pathology and clinical therapies [53].

Galectin-3 as a Biomarker in Breast Cancer

The key role of galectin-3 in breast cancer biology supports its evaluation as a biomarker. Numerous studies have examined prognostic and predictive value within different tumor subtypes, along with diagnostic testing of either circulating galectin-3 levels or tumor expression. Circulating galectin-3 is increased in breast cancer patients compared with healthy controls. Serum levels correlate with Ki-67 expression, disease stage, tumor burden, and tumor aggressiveness, and are linked to metastasis and recurrence. Invasive lobular breast carcinoma is characterized by higher serum levels relative to invasive ductal breast carcinoma. Tissue and serum levels predict cancer-specific survival independently of other covariates. Reduced galectin-3 expression is associated with poorly differentiated tumors and worse prognosis, consistent with a protumorigenic role. In triple-negative breast cancer, tissue levels are negatively correlated with overall survival, while circulating levels predict response to neoadjuvant chemotherapy [53,54].

However, results are inconsistent. Serum levels are higher in triple-negative than in non-triple-negative breast cancer; higher levels in breast cancer with distant metastasis compared with earlier stages have been reported. Predictive value may depend on immune environment expression: lower levels during neoadjuvant chemotherapy indicate poorer response in patients with high intratumoral FoxP3+ T-regulatory cells and CD68+ macrophages but better response in other individuals. Galectin-3 expression predicts prognosis only in triple-negative breast cancer receiving neoadjuvant chemotherapy. Discordance between serum and tissue levels complicates clinical application. A galectin-3 signature approach provides reliable prognostic stratification. Further collaborative efforts are needed to overcome limitations and establish clinical utility for therapeutic response prediction [54].

Diagnostic and Prognostic Implications

Breast cancer remains the second leading cause of cancer death in women, underscoring the urgent need for prognostic biomarkers that can predict patient outcomes and therapeutic efficacy. Several studies indicate that high levels of galectin-3 in tumor

tissue, plasma, and serum are frequent findings in breast cancer patients [55]. The association of elevated galectin-3 levels with an unfavorable clinical prognosis for breast cancer patients has been recognized; the lower the disease-free survival rate remains after the first five years following surgery, the higher the galectin-3 levels become. Determining the serum and plasma levels of galectin-1, galectin-3, and galectin-9 in breast-cancer patients and health controls indicates that, although there have been biopsies of tissue specimens arranged during treatment, it can be a complex and challenging task; monitoring circulating levels of soluble galectin-3 could still offer valuable assistance. It has been demonstrated that circulating galectin-3 can serve as a predictive biomarker for both neoadjuvant therapy response and residual disease in triple-negative breast-cancer patients. Assessing galectins in the tumor microenvironment can unveil more details regarding tumor progression and might help to stratify patients into different subtypes [56].

Dissemination of circulating tumor cells (CTCs) to distant organs marks the initiation of metastatic spread in breast cancer. CTC can contribute to the development of metastasis. Breast-cancer patients without CTCs at diagnosis do not later present metastatic disease, strengthening the proposed correlation between CTC and metastasis. Galectin-3-positive CTCs are present in almost all breast-cancer patients with clinically evident metastasis. Galectin-3 acts as a regulatory signal for the metabolic state of tumor cells, guiding them between dormancy and proliferation. Consequently, CTCs bearing activated galectin-3 either remain dormant or regain proliferative capacity at potentially metastatic sites [56].

Predictive Value for Therapy Response

Evidence supports galectin-3 as an important mediator of therapeutic resistance in breast cancer, and its expression profile is associated with resistance to endocrine therapy. Galectin-3 is implicated in the development of trastuzumab resistance in HER2-enriched breast cancer, as well as in resistance to radiation therapy and immune checkpoint inhibition [57].

Hormonal resistance, a crucial step in breast cancer progression and relapse, characterizes endocrine therapy failure and is more frequently observed in ER-positive breast cancer. High tumor galectin-3 levels correlate with reduced sensitivity to selective estrogen receptor modulators and selective and nonselective estrogen receptor downregulators in hormone receptor-positive breast cancer cells, likely through attenuation of the apoptotic pathway. In animal models with ER-positive tumor xenografts, galectin-3 knockdown or administration of the small-molecule galectin-3 inhibitor gallol recovers the response to tamoxifen. Concordantly, positive galectin-3 expression in human ER-positive breast cancer is associated with shorter disease-free intervals in patients treated with adjuvant tamoxifen [57].

Circulating tumor cells (CTCs), identified in the blood of cancer patients, contribute to breast cancer metastatic recurrence. An active galectin-3 pathway, through CTC-expressed galectin-3 and macrophage-expressed galectin-3 binding protein, supports CTC viability and decreases the risk of brain metastatic recurrence after complete tumor resection. Targeting the galectin-3 pathway in this CTC-host interaction may have therapeutic potential. In HER2-positive breast cancer, galectin-3 glycosylation, mediated by Golgi-specific sialyltransferase-6, promotes trastuzumab resistance and enhances the invasive capacity of HER2-enriched breast cancer cells. High galectin-3 expression in the stroma is associated with poor overall survival and breast cancer-specific survival and may independently predict poor prognosis for patients treated with neoadjuvant therapy [58].

Therapeutic Targeting of Galectin-3 in Breast Cancer

Tumoral galectin-3 expression constitutes a resistance mechanism to endocrine therapy in ER+ breast cancer, supporting the development of therapeutic strategies aimed at inhibiting galectin-3 function during adjuvant therapy. Downstream of PD-1 blockade, MDA-MB-231 cells express galectin-3, which supports immune evasion by upregulating PD-L1 in an autocrine manner. The research collective observed that galectin-3 blockade sensitizes MDA-MB-231 breast cancer cells to immune attack in an experimental model.

Moreover, combination treatment with a galectin-3 antagonist and anti-PD-1 antibody reduced tumor burden and increased survival compared to anti-PD-1 antibody alone in mice, further validating galectin-3 as a therapeutic target [59].

In addition to immune evasion of the primary tumor, upregulation of PD-L1 in CTCs by galectin-3 also represents a mechanism of immune adaptation during CTC dissemination. Altered expression of immune checkpoint molecules in CTCs and their relevance as a predictive factor have thus far been overlooked. CD47 acts as a "don't eat me" signal that protects tumor cells from macrophage phagocytosis. CTCs from breast cancer patients express elevated levels of PD-L1 and CD47, contributing to immune evasion during tumor dissemination and representing promising therapeutic targets. Combined blockade of PD-L1 and CD47 on CTC–macrophage co-cultures enhances macrophage phagocytosis. Galectin-3 upregulates CD47 expression in CTCs. These studies underscore the potential of targeting galectin-3 to dampen CTC immune privilege and facilitate their clearance during metastasis [60].

Breast cancer patients with lung metastasis show upregulation of PD-L1 in CTCs and abundance of galectin-3 in the primary tumor, suggesting the involvement of tumor-derived factors in PD-L1 expression in CTCs. Breast cancer-associated galectin-3 expression creates a favorable inflammatory microenvironment for the formation of inflammatory pre-metastatic niches and constitutes an important risk factor for lung metastasis. Recent evidence highlights the role of galectin-3 in restraining the apoptotic response to targeted therapies in HER2+ breast cancer. Inhibition of galectin-3 cooperates with lapatinib in inducing apoptosis in HER2+ breast cancer. Overall, these studies underscore the importance of galectin-3 in breast oncogenesis and support its development as a therapeutic target [61].

Small Molecule Inhibitors and Biologics

Small molecule inhibitors as well as biologics, such as monoclonal antibodies and antisense oligonucleotides, targeting galectin-3 have shown preclinical anticancer efficacy in multiple tumor types Other strategies to silence galectin-3 expression, for instance, using adenoviral vectors or nucleofection, have also yielded promising results. Gal-3 inhibitor-mediated cell death involved electronegative changes in the cancer cell surface and penetrated-neutralizing gal-3 carbon-ion beams. Enforced expression of gal-3 shRNA suppressed galectin-3 levels, led to cell cycle arrest and apoptosis, and increased chemotherapy sensitivity of cancer cells. Additionally, gal-3 downregulation in the tumor milieu improved immunogenicity by rescuing the NKG2D pathway [62].

Gal-3 inhibitors have recently entered phase I and II clinical trials for advanced cancers. The gal-3 antibody GB1211, eliciting an antagonistic effect on the interaction of gal-3 with its high-affinity receptors, was the first novel therapeutics designed to block gal-3-mediated immunosuppression in solid tumors. In patients with advanced cancer receiving single-agent GB1211, no dose-limiting adverse events were observed during safety monitoring and preliminary evidence of a clinical response was reported. Furthermore, the combination of Fortis Tibialis Purpureus and autoantibodies targeting Gal-3 has been suggested as a promising approach against tumor progression. The availability of tools capable of ameliorating the pharmacologic inhibition of gal-3 is thus warranted. In this context, bitter melon polysaccharide extract appears to represent a potential gal-3 inhibitor that reduces gal-3 expression [62].

Combination Strategies to Overcome Resistance

The use of galectin-3 inhibitors in combination with other agents may provide an avenue to overcome therapeutic resistance in breast cancer. Recent preclinical studies have reported that the combination of therapy resistance inducers, such as doxorubicin or paclitaxel, with small molecule inhibitors of galectin-3 activity (e.g., OTX008, GR-MD-02) resulted in synergistic inhibitory effects on the viability of breast cancer cells. On the other hand, galectin-3 induction in Doxorubicin-resistant MCF-7 cells has been proposed as a therapeutic target for restoring sensitivity to the drug; knockdown of galectin-3 restores doxorubicin sensitivity and downregulates the expression of several well-known doxorubicin resistance-related genes, such as annexin A6 and epiregulin. As previously

discussed (see Section 5.2), targeting galectin-3 in RBP1-overexpressing resistant cells aids in reversing the drug resistance phenotype [63].

Enhanced expression of galectin-3 in the tumor microenvironment has also been associated with immunotherapy resistance. In a lung cancer preclinical model, disruption of galectin-3/cXCR4 interactions with PRO171 significantly improved the therapeutic efficacy of an anti-PD-1 antibody in mice with established tumors. Such promising results warrant explorations of galectin-3 targeting in combination with PD-1 blockade in breast cancer. Notably, treatment with PTX-2, an inhibitor of galectin-3–mediated immune suppression, has been shown to enhance the anticancer effects of α-PD-1/α-CTLA-4–based immunotherapy in melanoma and non-small-cell lung cancer. Combination strategies targeting galectin-3, therefore, appear especially attractive in the context of ablating both the intrinsic resistance of the tumor and the immune evasion associated with advanced disease [64].

4. Conclusion

Analysis has shown that galectin-3 functions as a molecular mediator in breast cancer, integrating structural-functional features with evidence implicating it in tumor initiation, progression, metastasis, and resistance to therapy. As an abundant and pleiotropic protein produced by multiple cell types in the tumor microenvironment, its differential expression pattern in breast cancer depends on intrinsic Tumor Biology and the immune composition of the stroma. A multitude of mechanisms likely accounts for the key roles of galectin-3 in promoting breast cancer and preclinical trials have demonstrated the therapeutic benefit of galectin-3 targeting, paving the way for clinical translation.

Importantly, galectin-3 operatives have been identified that could serve as potential biomarkers of cancer therapy response. Nevertheless, current knowledge remains incomplete, especially regarding the diverse mechanisms underlying the contribution of galectin-3 to breast cancer biology. Continued research focused particularly on integrative, multidisciplinary approaches should advance understanding of galectin-3 in breast cancer and support the development of novel therapeutic approaches.

Funding

There is no funding

Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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