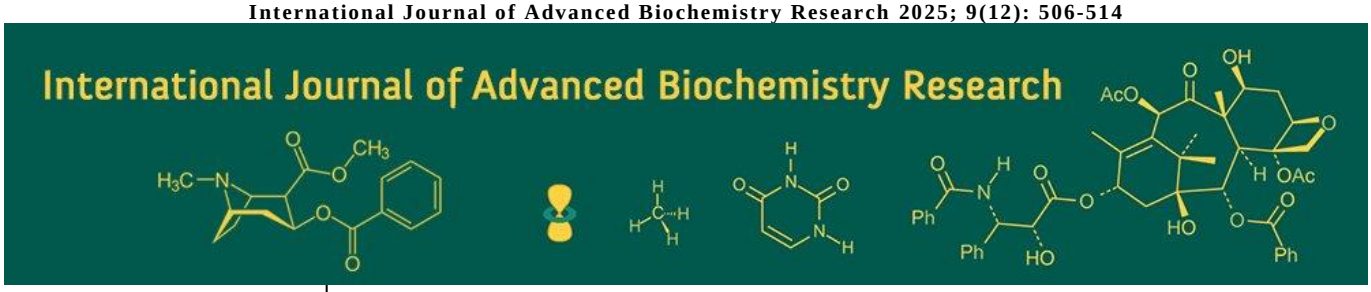

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The role of galectin-3 in cancer development and progression

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Abstract
Based on to the hallmarks of cancer, there are six distinct capabilities contribute to the development and progression of cancer. Developments in the conceptual knowledge of cancer prevention over the last years have led to the recent suggestion that metabolic reprogramming and immunological evasion be agreed as new hallmarks. The target that epigenetic changes be considered another characteristic of cancer, and hence an extra focus for research in the next generation of cancer treatments. Galectin-3, a 31 kDa intracellular and extracellular lectin that interacts with extracellular matrix proteins, intracellular glycoproteins, and cell surface molecules. Galectin-3 is expressed in multiple cell types and modulates a variety of biological processes associated with tumorigenesis. These processes include cell adhesion, proliferation, resistance to apoptosis, angiogenesis, metastasis, and immune response. Its unique ability to be intracellular and extracellular allows it to participate in a wide range of signaling pathways in tumor microenvironments. Several studies have demonstrated high levels of Galectin-3 in cancers, making it a potential diagnostic and prognostic marker. Galectin-3 has also been targeted as a novel strategy for treating cancer, but its clinical applications remain in their infancy. In this review, presented the discovery, biological functions, and oncological relevance of galectin-3 in cancer.

Keywords: Galectin-3, Biomarkers, Cancer, Tumor Microenvironment, Cancer Therapy

Introduction
Galectin-3 (Gal-3) is a member of the galectin family and it's the only "chimera-type" galectin, it is a beta-galactoside-binding lectin encoded by the LGALS3 gene, located on chromosome 14 locus q21-22 [1-4]. Galectin has a distinctive structure consists of two distinct domains: N-terminal domain (ND) which consists of a repetitive collagen-like sequence enriched in glycine, proline, and tyrosine and a C-terminal domain (CD) [5]. A trait exclusive to the galectin family and highly conserved across species is the 12-amino acid leader sequence with a casein kinase I phosphorylation site found in the N-terminal domain (ND) of Galectin-3. Both the secretion of Galectin-3 and nuclear translocation depend heavily on this domain [6]. The MMP-2 and MMP-9 matrix metalloproteinases can proteolyze the ND of galectin-3, which is necessary for galectin-3 multimerization [7]. The C-terminal domain (CD), on the other hand, performs the binding to the carbohydrates by binding to the poly-N-acetyllactosamine residues on laminin. This contact is essential to the pathogenesis of cancer because it has been directly related to tumor invasion and metastasis [6]. The C-terminal part, the carbohydrate recognition domain (CRD), is a globular domain containing about 130 amino acids, including a conserved NWGR (Asn-Trp-Gly-Arg) motif that enables galactin-3 to bind to B -galactosides, making galactin-3 an anti-apoptotic protein.The B-cell lymphoma 2 (Bcl2) family of apoptotic regulators also features this NWGR motif which grants galactin-3 its anti-ap [7]. Moreover, angiogenesis and tumor growth are activated by the cleavage of the N-terminal domain of the tumor microenvironment especially in breast cancer [8].

Tissue distribution of galectin-3
Galectin 3 is synthesized in the cell cytoplasm and moves between the cytoplasm and the nucleus. Additionally, a non-classical extocytosis pathway can secrete it to the cell surface and biological fluids [7]. Galectin-3 is highly expressed in human tissues, including immune cells, epithelial cells and sensory neurons. However, galectin-3 exhibits a more particular pattern of expression in the early stages of human embryogenesis, primarily in the liver, kidney, chondrocytes, and epithelia [7].

Functional properties of intracellular galectin-3

The nuclear and cytoplasmic localization of Galectin-3 is well documented and is determined by cell type, proliferation, environmental conditions, and neoplastic transformation. The intracellular roles of Galectin-3 are greatly determined by its particular localization within the cell [9].

Galectin-3 in cytoplasm

Advanced molecular biology techniques have revealed Galectin-3 protein to be one that binds to a large number of cytosolic proteins, influencing several critical cellular functions like regulation of apoptosis, cell survival, and intracellular transport. Galectin-3 binds Bcl-2, one of the crucial apoptosis regulators, via its CRD and consequently provides anti-apoptotic effect. It also interacts with CD95 (Fas/APO-1), a death receptor, and with Nucling, another protein involved in regulating apoptosis [10, 11]. Galectin-3 is linked with Alix/AIP1, which is a cytosolic protein involved in apoptotic signaling, highlighting its role in controlling programmed cell death [12]. Furthermore, its effects on K-Ras protein [13, 14] and Akt protein [15, 16] further supported the role of cytosolic galectin-3 in the control of cell proliferation, differentiation, survival, and death. It was demonstrated that activated K-Ras (K-Ras-GTP) selectively binds to galectin-3.

Synexin (annexin VII), a 51-kDa calcium- and phospholipid -binding protein, interacts with galectin-3 in human breast epithelial cells. This interaction is essential for Galectin-3's perinuclear translocation to the mitochondrial membrane, where it carries out its anti-apoptotic function. When synexin is downregulated, Galectin-3 cannot reach the mitochondria, negating its anti-apoptotic function. These findings indicated that synexin may play a role in the intracellular trafficking of galectin-3 and identified mitochondria as a novel galectin-3 localization site [17].

A number of cytokeratins containing terminal N-acetylgalactosamine residues have been suggested as potential Galectin-3 ligands. However, although *in vitro* studies demonstrate this interaction, *in vivo* research is lacking [18]. A yeast two-hybrid screen identified Chrp, a cytoplasmic cysteine- and histidine-rich protein, as a Galectin-3 binding partner. Although both proteins are ubiquitously expressed in the cytoplasm, Chrp is also found at the nuclear envelope. This suggests that Galectin-3 possesses multiple independent binding sites within its carbohydrate recognition domain (CRD) to bind to various intracellular structures [19].

Nuclear galectin-3

Galectin-3 has been localized to the nucleus, even though it lacks a recognized nuclear localization signal, and the mechanism by which it is imported into the nucleus is not fully elucidated. Mutagenesis experiments have provided conflicting evidence for the minimal sequence required for its localization to the nucleus. While some observations suggest that the first 11 amino acids are required for nuclear import [20], other experiments indicate that the carbohydrate recognition domain (CRD) is crucial [21]. The nuclear localization of Galectin-3 is also found to be cell-type dependent, with some cells not expressing it in the nucleus even if there are high concentrations in the cytoplasm [22]. On the other hand, Galectin-3 export from the nucleus is clearer. It occurs through a rapid and selective process that is inhibited by leptomycin B, which keeps the nuclear export signal (NES) of Galectin-3 from interacting with the chromosome maintenance region 1 (CRM1) nuclear export receptor [9]. Galectin-3 in the nucleus has distinct functional processes. It is associated with ribonucleoprotein complexes and plays a role in pre-mRNA splicing and assembly of the spliceosome [23, 24]. It has also been shown to play a role in modulating gene transcription via its binding with transcription factors CREB and Sp1 to enhance the activation of cell cycle genes cyclin D1, cyclin A, and cyclin E [25]. Galectin-3 also mediates TTF-1, thyroid-specific transcription factor, to enhance its DNA-binding activity and thus thyroid proliferation [26].

Furthermore, Galectin-3 is also a crucial part of Wnt/β-catenin signaling since it has direct interactions with β-catenin and its regulatory proteins, such as axin, and hence influences phosphorylation events crucial for pathway regulation. Galectin-3 has been shown to enhance GSK-3β-dependent phosphorylation, further showing its role in Wnt signaling [9]. Additionally, Galectin-3 affects CBP70, which is a glucose-specific lectin, in lactose-dependent association, rendering it the sole reported nuclear Galectin-3 partner with such an association. These findings emphasize the multifunctional roles of nuclear Galectin-3 within RNA processing, transcriptional regulation, and intracellular signaling cascades, again demonstrating its more widespread influence on cellular function and disease process [9].

Extracellular Functions of Galectin-3

Although Galectin-3 has no known conventional signal of secretion, it is extensively constituted in the extracellular space, where it is known to have important roles in cell adhesion, cell signaling and immune regulation. Unlike conventional secretory proteins, Galectin-3 bypasses the ER/Golgi-dependent pathway and is instead exported through unconventional routes. One proposed pathway is through vesicle-mediated secretion, although the specific vesicles have not been characterized. Another mechanism includes exosomes, as Galectin-3 is present in exosomes secreted from dendritic cells, suggesting a role in antigen presentation and immune regulation [9]. When secreted, extracellular Galectin-3 interacts with cell surface receptors and extracellular matrix components modulating key biological processes such as cell adhesion, immune response, organogenesis, and angiogenesis. It also plays a role in tumor invasion and metastasis by modulating cell-cell and cell-matrix interactions [27-32]. Galectin-3 is also internalized via endocytosis in a lactose-dependent manner and facilitates the internalization of β1 integrins, advanced glycation end-products (AGEs), and modified low-density lipoproteins (LDL) [33, 34].

Galectin 3 in cancer

Galectin 3 is extensively expressed in human tissues, it has a role in a variety of biological processes, including immune system modulation, mRNA splicing, cell adhesion, proliferation, apoptosis, and embryogenesis [7]. In cancer and precancerous situations, changes in galectin-3 expression and subcellular and intercellular localizations are frequently seen [35]. Additionally, when adenoma turns into carcinoma, there is a general change in the location of galectin-3 from the nucleus to the cytoplasm. Galectin-3 may play a role in carcinogenesis, angiogenesis, and tumor metastasis [36].

Intracellular galectin-3 overexpression inhibits apoptosis, accelerates the cell cycle, and encourages neoplastic transformation. Tumor cell adherence to extracellular matrix (ECM) is improved by extracellular galectin-3, which also facilitates tumor cell escape from the primary tumor locations [7].

Galectin-3 is a crucial component of the nucleus in regulating the expression of the tumor-related genes, including cyclin D1, TTF-1, and MUC2, in the nucleus, which are probably associated with tumor growth [3].

The role of galectin 3 in selected cancers

Gal-3 role in pancreatic cancer has been well investigated on experimental basis in an attempt to explain the molecular mechanism and potential therapeutic value of the protein. These studies have given significant insights on how the Gal-3 can be involved in tumor growth, metastasis, and resistance to treatment among other characteristics of pancreatic cancer. In a study by Xie et al., the expressions, and clinical significance of tissue and serum Gal-3 in pancreatic cancer have been analyzed by [37]. The researchers examined the gal-3 expression in the pancreatic cancer cells and in serum of pancreatic cancer patients. They found that the pancreatic carcinoma tissues had significantly higher levels of Gal-3 expression as compared to the surrounding non-cancerous tissues. Moreover, the serum Gal-3 concentration was also greater in people with pancreatic cancer than in healthy controls. The paper also investigated the correlation between the clinicopathological features and Gal-3 expression in patients with pancreatic cancer. They discovered that an overall poor survival, metastases in the lymph nodes and high tumor stage were all associated with a high expression of Gal-3 in tumor tissues. Similarly, we found that there was an association between a rise in the level of blood Gal-3 with distant metastases, lymph node metastases, and tumor size.

To determine the diagnostic and prognostic capabilities of Galectin-3 (Gal-3) and PTEN, Jiang et al. carried out a study to examine their expression in gastrointestinal cancers, pancreatic ductal adenocarcinoma (PDAC), and pancreatic neuroendocrine neoplasma (PNNs) using fine-needle aspiration cytology (FNAC). The immunocytochemistry results revealed that PTEN was slightly expressed in PDAC compared to PNNs and gastrointestinal tumors whereas Gal-3 was highly expressed in PDAC. The implication of these findings is that the difference in PTEN and Gal-3 expression can be employed as a diagnostic marker to distinguish PDAC with other types of tumors. Also, Gal-3 expression in PDAC patients was identified to be positively correlated with decreased overall survival rate, thus, indicating that it could be utilized as a predictive biomarker [38].

Coppin et al. [39] carried out a study aimed at comparing diagnostic value of CA- 125 versus Galactin-3 (Gal-3) in the differentiation between pancreatic ductal adenocarcinoma (PDAC) and non-malignant pancreatic conditions. Although the tests on both biomarkers have been conducted in pancreatic disease setting, the study revealed that CA-125 was more diagnostic than Gal-3. In particular, CA-125 concentrations were much higher in PDAC patients but there was no significant difference in Gal-3 levels in malignant and non-malignant conditions. Such results support the idea that CA-125 could be a better choice of biomarker to be used in differentiating PDAC and benign pancreatic diseases.

The study argued that CA-125 responded better to diagnostic differentiation between PDAC and non-malignant pancreatic illness when used in combination with the universal biomarker CA19-9. The CA-125, CA19-9 enhanced the diagnosis whereas Galectin-3 (Gal-3) did not. These findings suggest that a biomarker panel that comprises CA-125 and CA19-9 can be used to improve the diagnosis of PDAC.

Yi et al. [40] investigated the clinical value of Galactosidase-3 (Gal-3), as a screening, early diagnosis, prognosis, and follow-up therapy in pancreatic cancer by measuring the serum levels of the protein using a time-resolved fluorescence immunoassay. The level of Gal-3 reduced significantly in the patients who went through radical surgery after one month of surgery and no noticeable change was observed in the patients who were palliatively resected. Also, recurrence was linked to the consistent or progressive Gal-3 levels in those who underwent significant surgery. Retrospective analysis indicated potential of Gal-3 as a biomarker in detecting early markers, classification of risks, and monitoring of therapy in pancreatic cancer as it was found that it was highly predictive of survival in three years.

Gaida et al. [41], discussed the Gal-3 expression in normal pancreatic tissue and PDAC tissue. They discovered that Gal-3 was significantly more expressed in PDAC and related to a low prognoses and worse overall survival rate. They indicated that Gal-3 plays a role in the pathogenesis of PDAC and could be used in treatment, as well as prognostic. All these findings contribute to the fact that Gal-3 is an important player in the pathophysiology of pancreatic cancer and its clinical use.

Their findings indicate that Gal-3 expression is significantly elevated in the PDAC tissue as compared to normal pancreatic tissues, therefore, Gal-3 would be a beneficial variable to assess the tumor aggressiveness and prognosis in PDAC (Shimamura et al.,) [42]. Gal-3 was also significantly associated with high levels of lymph node metastasis and tumor poor stage. These findings enhance our knowledge of the role of Gal-3 in the development of pancreatic cancer and its possible treatment value.

In their study of patient and healthy control blood, Shimura et al. [43] showed that the prognostic and diagnostic potential of circulating Galectin-3 (Gal-3) are elevated in cancer patients and that they are correlated with the progression of the tumor with the higher level in the advanced cases of cancer. Moreover, they have found that high Gal-3 levels possess a prognostic value, as well as have been associated with worse overall and disease-free survival. Based on the findings, Gal-3 in circulation may be a valuable biomarker in the diagnosis and prognosis of pancreaticobiliary cancer.

Yang et al. [44] examined Galactin-3 (Gal-3) play a role in pancreatic ductal adenocarcinoma (PDAC) using a genetically modified mouse model. Gal-3 accelerates tumor proliferation and immune evasion by altering the tumor microenvironment, as their findings revealed. Gal-3 knockdown promoted survival, tumor growth inhibition and antitumor immunity.

The paper established also that the CXCL12 overexpression is the compensatory response to Gal-3 loss. It is important to note that PD-1 immune checkpoint and CXCL12-CXCR4 inhibition with Gal-3 inhibition caused a significant increase in immunotherapy response and prevent the development of PDAC.

Based on these outcomes, Gal-3 plays a vital role in the regulation of PDAC aggression and immune suppression. Gal-3 combined with immunotherapy and inhibition could be a distinctive combination to improve the outcomes of patients.

To determine the oncogenic nature of Galactose lectin-3 (Gal-3) in pancreatic cancer cells, Hann et al. [45] conducted a detailed study. Their findings did not always agree with previous literature that Gal-3 is a tumor-growth promoter, in contrast with other researchers. Knockdown tests of Gal-3 expression did not have significant effect on cell migration or cell invasion, cell apoptosis, or cell proliferation. Moreover, particular relationships between Gal-3 and significant carcinogenic pathways by EGFR, p53, or KRAS stimulation were not found.

However, Gal-3 binding protein (Gal-3BP) was identified as a key player in the development of pancreatic cancer in a different study. Researchers found that pancreatic ductal adenocarcinoma (PDAC) had higher levels of Gal-3BP than breast cancer using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Its upregulation was verified by immunohistochemical analysis in PDAC tissues and plasma samples. Gal-3BP activates the EGFR-Myc signaling pathway, which facilitates tumor development, migration, and metastasis, according to functional study. These results demonstrate that while Gal-3BP would be a good target for the development of novel therapeutic strategies, Gal-3 itself would not represent a significant carcinogenic component of PDAC.

Da Silva Filho et al. [46] looked into how starvation and hypoxia affected the expression of Galectin-3 (Gal-3) in pancreatic cancer cells. Gal-3 expression and secretion were elevated in both circumstances, indicating that stresses in the tumor microenvironment may regulate Gal-3 levels. These findings define Gal-3 as a potential target of therapy that is controlled by tumor microenvironmental signals and contribute to the understanding of the molecular mechanisms of the progression of pancreatic cancer.

The study of Galectin-3 (Gal-3) role in the activation of pancreatic stellate cells (PSCs) and interaction with PDAC cells was conducted by Zhang et al. [47]. Gal-3 was demonstrated to be upregulated in tumor-associated stroma cells and PDAC cells. The Gal-3 stimulated the pathway of ITGB1/ILK/NF- kB in PSCs, which enhanced IL-8 synthesis and, therefore, tumor-stroma crosstalk and pancreatic cancer progression.

Additional examination showed that Gal-3 also suppressed the proliferation of V 9 V delta 2 T cells, which was an immunosuppressive phenomenon. The PDAC cells secreted Gal-3 that inhibited the development of T cells. When the levels of Gal-3 were increased, it partially recovered its immunoevasive activity.

The therapeutic effect of the safflower polysaccharide HH1-1 was examined separately of the above-mentioned research. It was found to inhibit Gal-3 and act in the Gal-3/EGFR/AKT/FOXO3 pathway. Based on this finding, Gal-3 inhibition can disrupt tumor-stroma interactions, enhance immunity, and should be a therapeutic option to treat pancreatic cancer.

Gonnermann et al. [48] also examined the effect of the Galectin-3 (Gal-3) secreted by PDAC tumors on Gamma delta T cell (or 4-delta T cell), which is a subpopulation of T cells, demonstrated that the release of gal-3 had no effect on the ability of the cells to kill cancer cells, but it inhibited their proliferation. It was found that the mechanism of this inhibition was the interaction of Gal-3 with some γδ T cell receptors. These findings emphasize the immune evasion of Gal-3 by PDAC tumors and underline the importance of understanding the interactions between immune cells and cancer to be able to come up with effective immunotherapies.

Gastric cancer

Gastric cancer (GC) is the second cancer that causes the most number of deaths globally and is the fourth most prevalent form of cancer [49]. The clinical relevance of serum galectin-3 levels in patients with gastric cancer was investigated by Tas et al. [50]. The results indicated no significant difference in baseline serum galectin-3 levels between gastric cancer patients and healthy controls. Older patients exhibited higher levels, but no correlation was found between galectin-3 levels and tumor characteristics, chemotherapy responsiveness, or survival outcomes. The findings suggest that serum galectin-3 lacks diagnostic, predictive, and prognostic value in gastric cancer.

Okada et al. [51] investigated the prognostic significance of galectin-3 expression in 115 gastric cancer patients. Immunohistochemical analysis revealed that reduced gal-3 expression correlated significantly with poor prognostic factors, including lymph node metastasis (p=0.0495), lymphatic invasion, and advanced pathological stage. Multivariate analysis identified low gal-3 expression as an independent prognostic factor Additionally, two single nucleotide polymorphisms (SNPs) were identified in the gal-3 gene, but no mutations were found. The findings suggest that gal-3 expression could serve as a valuable prognostic marker in gastric cancer, indicating that reduced expression is associated with unfavorable outcomes.

Kim et al. [52] investigated the role of galectin-3 in enhancing gastric cancer cell motility through the up-regulation of fascin-1, an actin-bundling protein. High levels of galectin-3 and fascin-1 were found in malignant gastric tissues, correlating with poor prognosis. Silencing galectin-3 reduced fascin-1 expression, altered cell morphology, and decreased cell migration and invasion by nearly 50%. Conversely, galectin-3 overexpression restored these effects. Mechanistically, galactin-3 binds with glycogen synthase kinase-3 (GSK-3 -1) and β-catenin and enhance their nuclear localization and fascin-1 promoter interaction. These results indicate galactin-3 to be a possible treatment target in gastric cancer progression with 73.7% of the patients having high levels of galactin-3.

Myazaki et al. [53]. This research performed an investigation on galactin-3 expression in 86 primary gastric tumors and 40 metastatic lymph nodes, where it is observed that 84 percent of tumors expressed galactin-3 positively, and the nuclear immunoreactive stain was observed in cancerous tissues (that had galactin-3 expression) to a higher degree than normal adjacent non-cancerous mucosa. It is important to note that an increase in galectin-3 levels was notable in papillary and poorly differentiated adenocarcinomas with respect to tumor progression (TNM staging). The lymph nodes which had a metastatic tumor displayed an increase of galectin-3 expression compared to the primary tumors, especially the poorly differentiated adenocarcinomas. The above results indicate that galactose-3 can be useful as a tumor marker of gastric cancer growth and metastasis in lymph nodes, with a particular focus on the subhistological

types. The paper suggests that more investigations should be conducted on the biological implications of galactin-3 in gastric malignancies.

Cheng et al. [54]. The paper examines the serum galactoside-3 (Gal-3) as a possible biomarker to gastric cancer (GC) through the measurement of concentrations in 87 GC, 53 benign gastric lesion, and 51 normal controls. Results show significantly higher Gal-3 levels in GC patients (18.32±7.25 ng/ml) compared to benign (10.04±3.47 ng/ml) and healthy controls (10.56±3.63 ng/ml, $p<0.001$). Gal-3 levels correlate with lymph node (P=0.001) and distant metastasis ($p<0.001$), but not with other clinical factors. ROC analysis indicates a sensitivity of 77.0% and specificity of 82.7% at a cutoff of 13.30 ng/ml. Although high Gal-3 levels did not significantly affect overall survival (P=0.099), the findings suggest Gal-3 could serve as a diagnostic marker for GC.

Leal et al. [49]. This study investigates the roles of annexin-A2 (ANXA2) and galectin-3 (GAL3) in gastric cancer (GC) among individuals from northern Brazil, highlighting their potential as prognostic biomarkers. ANXA2 mRNA was up-regulated in 32.14% of gastric tumors, correlating with lymph node metastasis (P = 0.016), while GAL3 protein was reduced in 50% of tumors, associated with distant metastasis (P = 0.038). ANXA2 and GAL3 localization in GC cell lines was induced by immunofluorescence. The results indicate that deregulated expression of these proteins help in an invasive role in GC, which implies that it has a role to play in the study of gastric carcinogenesis and therapeutic target discovery.

Breast cancer

The galactinin-3 is a key molecule that has been identified to be linked with the metastatic activity of breast cancers globally as it plays a major role in mediating cell-cell and the extracellular matrix (ECM). Finally, the interactions facilitate metastatic growth because they enhance the survival of tumors, their invasiveness, and spread [55, 56].

It has been shown that the expression of galactin-3 is linked to the advanced tumor stage in the case of triple-negative breast cancer (TNBC), an active form of the disease characterized by the absence of HER2, progesterone, and estrogen receptors. As it was stated by Ram et al. [57], galectin-3 levels of TNBC are associated with resistance to drugs, stemness, and the epithelial-to-mesenchymal transition (EMT), which is considered to be significant influencing factors on tumor development and potential metastasis.

Galectin-3 is highly expressed across the subtypes of breast cancer. Poor survival outcomes are normally linked with high galactin-3 expression in TNBC but its prognostic worth in other subtypes remains uncertain. As one example, according to certain studies, the galectin-3 could be expressed more in cancer-associated fibroblasts (CAFs) than in tumor cells. Such localization in stroma has been related to the proliferation of the axillary lymph nodes and higher stages of the disease [55].

However, studies on the predictive value of galactin-3 in breast cancer have mixed evidence. Whereas there are studies that highlight its correlation with the negative effects, other studies show no significant association, not mentioning that the lack of it correlates with undesirable prognoses [58]. These conflicting findings indicate the complexity and circumstantiality of galectin-3 in breast cancer biology.

Galectin-3 is involved in the regulation of key cellular pathways, which promote breast cancer development. It is worth noting that it has an impact on expression of proteoglycans and glycosaminoglycans, which are critical components of the ECM that are involved in tumor cell invasion and migration. Galactin-3 knockdown disturbs these factors, which inhibit tumor growth and reduces the probability of metastasis [56]. Moreover, galactin-3 in TNBC cells has been co-expressed with mesenchymal markers, including vimentin, and this may indicate galactin-3 role in facilitating aggressive tumor phenotypes [57].

Although there is increased recognition of galactin-3 as a condition that contributes to the pathogenesis of breast cancer, studies continue to be conducted to establish its mechanisms of action and its possible application as a predictive biomarker.

Colorectal cancer

Galectin-3 is an important protein in the progression and metastasis of colorectal cancer (CRC) by modifying several cellular events that enhance tumor aggressiveness.

Its overexpression in colorectal cancer has been associated with increased invasion, impaired epithelial integrity as well as the establishment of a pro-metastatic tumor microenvironment.

The control of protease activity is one of the main ways that galectin-3 promotes tumor growth in colorectal cancer. According to Li et al. [59], galectin-3 stimulates the release of matrix metalloproteinases (MMPs) and cathepsin-B, which aid in the breakdown of the extracellular matrix and the compromise of the integrity of the epithelial monolayer. These impacts promote the invasion and spread of malignant cells.

Tumor budding, a crucial pathogenic characteristic associated with galectin-3, is the separation of individual cells or tiny clusters from the main tumor mass, a characteristic of aggressive tumor behavior. Elkady and Allam [60], discovered a correlation between enhanced tumor budding and elevated galectin-3 expression in colorectal cancer (CRC), indicating that the protein may play a role in the early spread of metastatic disease.

Furthermore, galectin-3 facilitates the intravasation and extravasation of cancer cells by modifying cell adhesion and movement. According to Erdoğan et al. [61], galectin-3 alters cell-cell and cell-matrix interactions, allowing tumor cells to move through the surrounding stroma and vasculature more effectively.

Galectin-3 has potential as a predictive biomarker in colorectal cancer from a clinical standpoint. Higher levels of galectin-3 were found to be significantly linked to lower overall survival (OS) and disease-free survival (DFS) in patients with colorectal cancer (CRC) in a cohort study by Wang et al. [62], highlighting the protein's potential as a prognostic marker.

Galectin-3 is being researched as a possible therapeutic target. Aureli et al. [4], investigated the effects of food-derived galectin-3 inhibitors and discovered that they successfully decreased galectin-3 activity in preclinical models. This suggests a new and practical method of modifying the harmful consequences of galectin-3 in colorectal cancer.

It is necessary to mention that in case of galectin-3 inhibition, it is not always followed by the consistently positive outcome. Several studies have reported variable

therapeutic responses and it is a fact that the role of galactin-3 in cancer biology is dependent on the context. These variations underscore the fact that further studies are necessary to determine the circumstances under which this galectin-3 targeting can be most effective and demonstrate the complexity of interactions of this protein in the tumor microenvironment.

Prostate cancer

Galectin-3 (Gal-3) also mediates immune suppression, cell cycle control, and tumor cell microenvironment and these are significant factors in the growth and metastasis of prostate cancer. Its involvement on tumor growth and metastasis can be emphasized by the over-expression it shows in both differentiated prostate cancer cells and cancer stem-like cells (CSCs). Gal-3 has the potential to become a therapeutic target of advanced prostate cancer due to its versatile roles [63].

A growing body of evidence suggests that Gal-3 inhibits an anti-tumor immune response that contributes to immune evasion in prostate cancer. Caputo et al. [63] state that Gal-3 is overexpressed in CSCs of prostate cancer, and it suppresses the growth of T cells and promotes an immunosuppressive environment. This immune suppression is what helps tumors to grow and metastasize in the first stages. Surprisingly, T cell activity was enhanced with the use of Gal-3 inhibitors, such as N-acetyl-D-lactosamine, thereby reasserting the role of Gal-3 in immune suppression and it is possible that Gal-3 inhibitors could be used to enhance immunological surveillance.

Gal-3 is also known to interfere with the tumor growth by modifying the cell cycle regulators. Wang et al. [64] said that Gal -3 induced cell cycle arrest and enhanced survival of cells by stabilizing p21, which is an inhibitor of cyclin-dependent kinases. It is the very stability that causes cancer cells to become even more aggressive and persistent. The relevance of gal-3 to promote aggressive tumor behavior was outlined by previous studies by Wang et al. [65] that established it reduced cell migration and invasion by inhibiting it.

Besides acting cell-intrinsically, GAL-3 promotes the growth of prostate cancer through altering the tumor microenvironment. Studies by Farhad et al. [66] and Gao et al. [67] indicate that gal-3 is associated with the high disease stage and unfavorable clinical outcome. It induces an immunosuppressive effect that enhances the growth of the metastases and protects the tumor cells against immunological attack. It is also interesting to find that Gao et al. [67] found that the cleavage form of Gal-3 is more prevalent in prostate cancer tissues and is associated with tumor growth and aggressiveness, which suggests that Gal-3 isoforms would be useful in diagnosis.

Although Gal-3 is evidently implicated in the immune-evasion and metastatic-promotion, its full inhibition may have unexpected outcomes. The inhibitor of Gal-3 could disrupt tumor homeostasis with the resulting tumor instability or resistance pathways because it maintains tumor cell survival and interactions in the microenvironment. Gal-3 should therefore be assessed as a therapeutic target in prostate cancer using a complex and context-specific method.

Lung cancer

Galectin-3 is over-expressed in lung cancer, particularly in the squamous cell carcinoma and non-small cell lung cancer (NSCLC) and the amount of galectin-3 has been associated with the progression of the disease and the likelihood of metastasis. The prevalence of its presentation in a variety of cancer subtypes of lung cancer underscores its importance in tumor biology and its potential utilization as a therapeutic target and as a biomarker. Galectin-3 has been identified to be highly expressed in 83.8% of non-small cell lung cancer and 87% of squamous cell carcinoma of the lungs suggesting a prevalence in malignant tissues [68, 69]. Another connection that galactin-3 has to tumor aggressiveness and systemic disease spread is the significant relationship between galactin-3 expression and nodal metastases and high pathological stage [69].

Galectin-3 is also a promising circulating biomarker besides its tissue expression. It has been identified that increased blood levels are linked with poor survival outcome among lung cancer affected patients and thus serve as to confirm its significance in early detection and prognosis [70].

It is also interesting to note that some genetic variations of galectin-3 can potentially modify the behavior of tumors and patient survival (Terzioğlu-Uşak et al.) [70], implying that genotypic profiling has the potential to enhance the predictive capacity of galectin-3. Galactoside-3, mechanistically, adds to the oncogenic phenotype of lung cancer through the increased tumor-initiating ability of cancer stem cells (CSCs). It has been shown that environmental exposures such as cigarette smoke enhance expression of galactin-3 in the lung tissue that can be involved in the development of cancer and also in the development of cancer by long-term remodeling tissue [71].

Conclusion

Within the context of this review, we have outlined various expression of galactin-3 in cancer cells and serum of patients. Numerous clinical trials on Gal-3 molecule are in progress to cure the severe neoplastic diseases. We have concluded that Galectins are crucial to the tumor biology, as well as potential therapeutic targets. The significance of Galectins in the early cancer diagnosis, personalized therapy, and forecasting therapeutic response is hard to overestimate. Altogether, the current investigation of Galectin roles and their application in cancer biology will remain a central area of study. With further understanding, the possibility to put these findings into clinical practice will bring huge improvements in the war against cancer.

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