# The Role and Action of Intracellular Galectin-3 in Cancer Cell Signalling and Behaviours

**Monu Kumar*[1], Raunak Rai[2] and Vinod Kumar Gupta[3]**

[1]School Of Life Science, University of Liverpool, Liverpool, United Kingdom, L35XA

[2]School of Science, Noida International University, Greater Noida-203201, India

[3]Life Science Division, Rapture Biotech International Pvt. Ltd., Noida-201301, India

***Corresponding author mail id: kkmonu746@gmail.com**

## Abstract

The multifunctional protein Galectin-3 (Gal-3) mainly contributes to the development of cancer progression, primarily by their intracellular functions, which are the regulation of apoptosis, modulation of autophagy, and key oncogenic signalling pathways that are PI3K/Akt and Wnt/β-catenin pathways. Additionally, Gal-3 interacts with LC3 and LAMP2, regulating autophagosome formation and enabling cancer cells to withstand metabolic stress. Moreover, its modulation of β-catenin nuclear translocation enhances cancer stemness and metastatic potential. Furthermore, it is also essential for extracellular functions such as promoting metastasis, immune evasion, and angiogenesis, which makes it a good potential biomarker and therapeutic target. Studies are ongoing on developing Gal-3 inhibitors, but the problems of selectivity and clinical efficacy have not been solved. This review systematically evaluates the intracellular mechanisms of Gal-3, its influence on tumour progression, the innovative therapeutic strategies that are being developed, and potential future directions. A deeper understanding of Gal-3's molecular mechanisms could promote the way for novel anti-cancer therapies and improve patient outcomes.

**Keywords:** Galectin-3, Cancer Cell Signalling, Apoptosis Regulation, Autophagy Modulation, Therapeutic Targeting

## 1. Introduction

Cancer is among the most common causes of death globally and requires a thorough understanding of its molecular mechanisms to develop successful protocols of prevention and treatment [1]. Among the numerous proteins implicated in cancer progression, the galectin family proteins now stand out as important cancer-progression proteins because they involve multiple cellular functions. A family of β-galactoside-binding proteins known as galectins bind to glycoproteins and glycolipids found in the extracellular matrix and on cell surfaces. These interactions modulate important biological processes such as proliferation, cell adhesion, migration, and apoptosis that are all critical for tumour progression [2] [3].

Among the members of the galectin family, Galectin-3 is thought to have a major role in the biology of cancer. Due to its overexpression, it has been linked to immunological regulation, tumour growth, and metastasis. Overexpression of Galectin-3 is significantly linked with poor prognosis in different cancers and thus represents a valuable biomarker and therapeutic target [4] [5] For instance, in lung cancer, Galectin-3 enhances tumour aggressiveness and metastatic potential. In prostate cancer, it promotes cell survival and apoptosis resistance, further driving tumour growth [6].

Galectin-3 is generally expressed both intracellularly and extracellularly and affects several oncogenic pathways. It acts in the nucleus and cytoplasm to regulate major signalling pathways like Wnt/β-catenin, inducing cell proliferation and survival gene transcription [7]. Extracellularly, it promotes tumour invasion via binding to extracellular matrix and cell surface receptors, enhancing cancer cell adhesion and migration [8] . This dual action provides Galectin-3, an important contributor to the pathophysiology of cancer. Figure. 1 illustrates the dual nature of Galectin-3's functions.

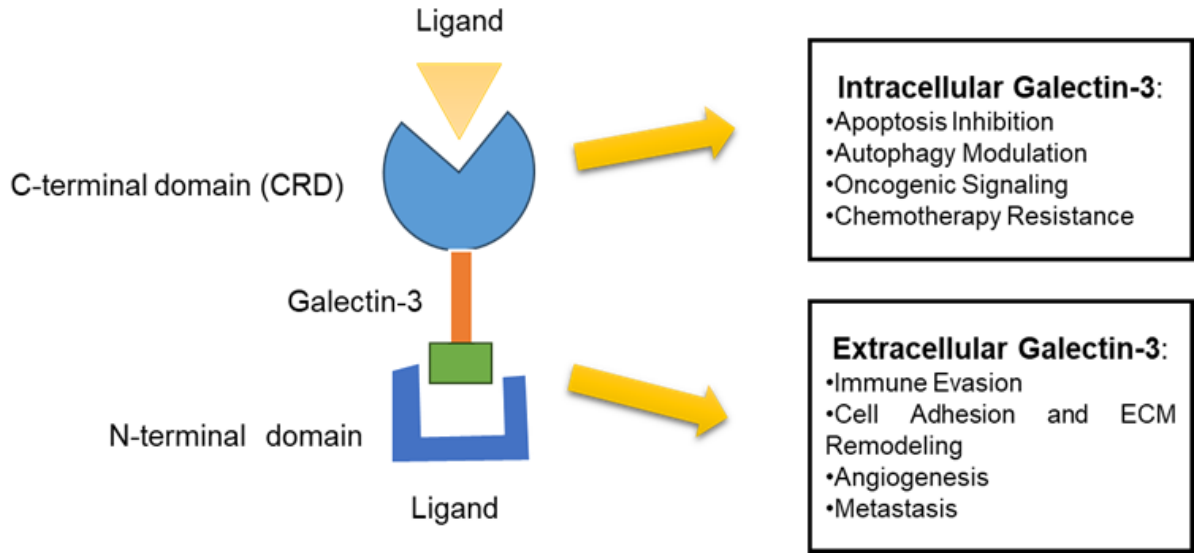


Figure 1: Functional roles of intracellular and extracellular Galectin-3 in cancer. (Intracellular Galectin-3 regulates apoptosis, autophagy, and oncogenic signalling, contributing to tumour progression and chemotherapy resistance. Extracellular Galectin-3 promotes metastasis, immune evasion, angiogenesis, and cell adhesion, facilitating cancer dissemination).

The abnormal expression of Galectin-3 is seen in various cancers, including breast, prostate, lung, and gastrointestinal cancers. In breast cancer, it has been shown to have a role in the development of cancer stem cell phenotypes responsible for tumour initiation and recurrence [9]. Its expression in prostate cancer is correlated with late stages of the disease and adverse clinical outcomes and can potentially be targeted for therapy [10]. Galectin-3 interacts with β-catenin to increase tumour invasiveness in lung cancer, whereas in gastrointestinal cancers, overexpression is linked to increased metastatic potential and poor prognosis.

With its extensive involvement in cancer progression, Galectin-3 is currently an attractive target in glycobiology, cancer research, and the development of therapeutic drugs. The goal of this review is to investigate the intracellular function of Galectin-3 in cancer cell signalling and behaviour along with its potential to act as a therapeutic target.

The purpose of this review is to investigate the role and mechanisms of intracellular Galectin-3 in cancer cell signalling and behaviour. Specifically, it aims to analyse how Galectin-3 influences key cell-based processes such as apoptosis, autophagy, and signal transduction within cancer cells. Additionally, Galectin-3's potential as a therapeutic target will be evaluated, highlighting its implications in cancer progression and treatment strategies.

## 2. Galectin-3 Structure and Functions

## 2.1 Structural Overview

Galectin-3 is particularly significant due to its multifunctional roles in both normal cellular processes and pathological conditions, especially cancer. Structurally, Galectin-3 is a 29–34 kDa protein composed of three distinct regions:

1. N-terminal domain (NTD): A short sequence of 12 amino acids that facilitates oligomerization, enabling the formation of functional multimers.
2. Collagen-like linker sequence: A flexible glycine- and proline-rich region that connects the N-terminal domain (NTD) to the C-terminal carbohydrate recognition domain (CRD). This linker is crucial for Galectin-3's structural flexibility and oligomerization, allowing interactions with intracellular and extracellular partners.
3. C-terminal domain (CRD): The primary carbohydrate-binding region, which mediates interactions with glycoproteins and glycoconjugates [1] [12].

Galectin-3, a member of the galectin family, is characterized by its unique chimera-type structure, which includes an extended N-terminal domain (NTD) and a carbohydrate recognition domain (CRD). The CRD allows Galectin-3 to bind to β-galactosides, a defining characteristic of all galectins [13]. However, what distinguishes Galectin-3 from other galectins is its ability to bind both glycan and peptide motifs, owing to the structural properties of its CRD and flexible collagen-like linker. This flexibility broadens Galectin-3's functional capacity, enabling its involvement in various oncogenic pathways, immune modulation, and extracellular matrix interactions [14] [15].

The CRD consists of a β-sandwich structure that interacts with glycans via a canonical site on the S-face and a non-canonical site on the F-face, enhancing its binding versatility [14]. Figure 2 illustrates the structural domains and polymerization potential of Galectin-3.

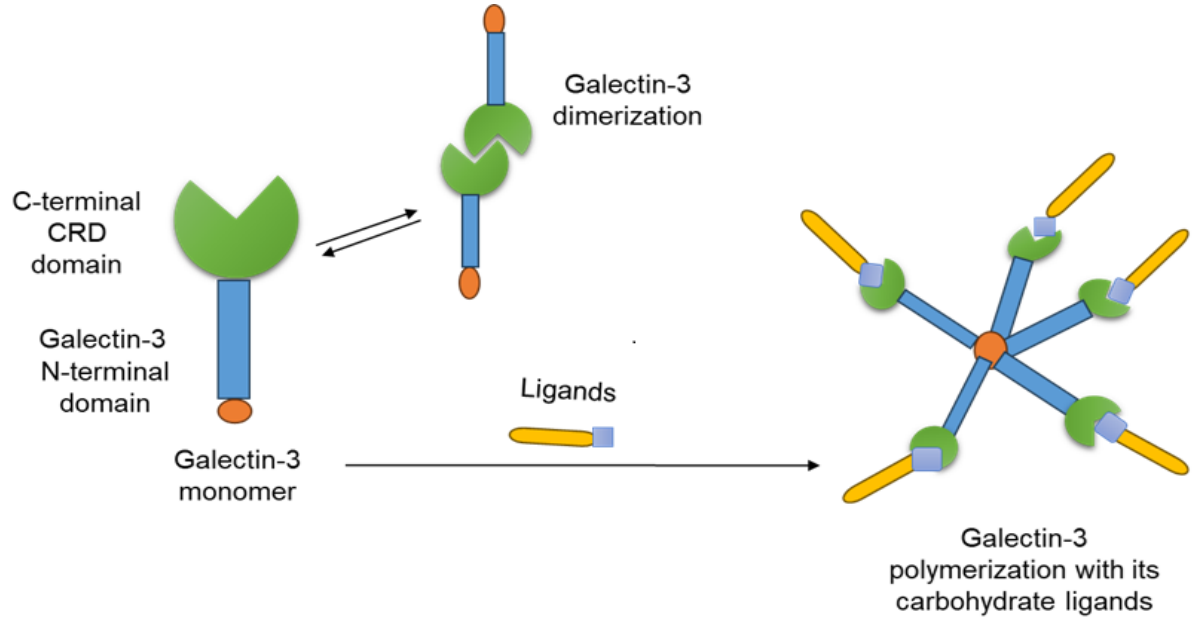


Figure 2: Structural representation and polymerization of Galectin-3. (Galectin-3 monomers can dimerize or form lattice structures with carbohydrate ligands, contributing to cell adhesion, immune modulation, and tumour progression).

The CRD plays a critical role in biological functions such as apoptosis and cell adhesion [16]. The unique structural and functional characteristics of galectin-3 are due to its long, intrinsically disordered, proline-rich N-

terminal tail (NT), which features several prolines [17]. The presence of NTD in Gal-3 is unstructured and has Pro-Gly-rich tandem repeats, which are like collagen [18] This domain contains two serine phosphorylation sites and accounts for 115 of the 250 amino acid residues of Galectin-3 [15]. The proline-rich NTD facilitates Galectin-3's ability to oligomerize and engage in dynamic interactions with glycoproteins and glycolipids [19]. Intracellularly, it regulates several processes such as cell survival and immunological responses by altering apoptosis and inflammatory signalling pathways [20], whereas extracellularly, Galectin-3 influences angiogenesis, immune evasion, and cell adhesion that facilitates tumour progression, particularly in the tumour microenvironment [21] [22]. Given its multiple roles, Galectin-3 is a promising therapeutic target for cancer, immune diseases, and chronic inflammation. Selective inhibitors may be developed to counteract its pro-tumorigenic effects [21].

### 2.2 Extracellular Functions of Galectin-3 in Cancer Progression

Extracellular Galectin-3 promotes immune evasion, metastasis, and angiogenesis, facilitating tumour progression through interactions with immune receptors, extracellular matrix (ECM) components, and angiogenic factors.

- Immune Evasion: Galectin-3 binds CD45 and CD71 on immune cells, suppressing T-cell activation and inducing apoptosis in activated T-cells, weakening immune surveillance [23] [24].
- Metastasis: By interacting with fibronectin, collagen IV, and laminin, Galectin-3 enhances cell adhesion and motility. It also activates integrins (α5β1) and matrix metalloproteinases (MMPs) to remodel the ECM and facilitate invasion [25] [26].
- Angiogenesis: Galectin-3 binds VEGF receptors (VEGFR-2) and αvβ3 integrins, stimulating endothelial migration and capillary formation, promoting tumour vascularization [27] [28].

While these extracellular roles drive tumour progression, this review primarily focuses on intracellular Galectin-3, which regulates tumour survival, therapy resistance, and oncogenic signalling.

## 3. Intracellular Mechanisms in Cancer Cells

### 3.1 Apoptosis Regulation

Galectin-3 (Gal-3) is recognized for its significant anti-apoptotic properties, particularly through its interactions with key apoptotic proteins. One of the most important interactions is with the anti-apoptotic protein Bcl-2, which is essential for cell survival. Gal-3 contains an NWGR motif similar to the BH1 domain of Bcl-2, which enables direct binding between Gal-3 and Bcl-2 [29] [30]. This structural similarity allows Gal-3 to function as a pseudo-BH1 domain protein, inhibiting pro-apoptotic signals.

At the molecular level, Gal-3 binds to Bcl-2 and prevents the activation and oligomerization of Bax/Bak, a key step in mitochondrial outer membrane permeabilization (MOMP). This interaction prevents the release of cytochrome c from mitochondria, blocking caspase activation and apoptosis initiation [31]. Studies indicate that Gal-3 possesses an NWGR motif, structurally similar to the BH1 domain of Bcl-2, which allows it to associate with Bcl-2 and regulate apoptotic signalling This interaction contributes to mitochondrial integrity, reinforcing cell survival under apoptotic stress conditions.

These mechanisms are particularly crucial in various cancers where high levels of Gal-3 correlate with increased resistance to apoptosis. Studies have shown that Gal-3 silencing enhances mitochondrial depolarization, making cancer cells more susceptible to chemotherapy-induced apoptosis In gastric cancer cells, Gal-3 depletion leads to reduced cell viability and increased caspase-3 activation, highlighting its role in chemoresistance [2]. Additionally, Gal-3 overexpression promotes the upregulation of stemness markers, enhancing the survival of cancer stem-like cells under therapeutic stress [33].

Gal-3's dual role as a tumour promoter and oncogene is tumour-type dependent. In malignant thyroid tumours and colon cancer, elevated Gal-3 levels are associated with tumour progression, while in breast cancer, its expression is often downregulated compared to normal tissue counterparts [34]. Moreover, Gal-3 is implicated in

resistance to chemotherapeutic agents such as cisplatin and etoposide, preventing apoptotic cell death by stabilizing Bcl-2 and reducing mitochondrial cytochrome c release [35].

Furthermore, Gal-3 influences cell cycle progression by modulating proliferating cell nuclear antigen and cyclin D1 proteins, which promote cell proliferation and survival [35]. This interplay between apoptosis inhibition and cell cycle regulation underscores the importance of Gal-3 in cancer progression and highlights its potential as a therapeutic target.

### 3.2 Modulation of Autophagy

Autophagy is a cellular degradation and recycling process that maintains homeostasis by breaking down damaged organelles and proteins, particularly under conditions of nutrient deprivation, oxidative stress, or chemotherapy [36]. It has been determined that galectin-3 is a crucial regulator of autophagy in cancer cells, allowing them to survive environmental and therapeutic stress.

At the molecular level, Gal-3 interacts with LC3, a key component of autophagosomes, facilitating autophagosome formation and subsequent degradation of intracellular components [36]. Additionally, Gal-3 regulates lysosomal function by interacting with LAMP2 (Lysosome-Associated Membrane Protein 2), a crucial protein required for the fusion of autophagosomes with lysosomes [37]. This interaction enhances lysosomal acidification and proteolytic activity, ensuring efficient degradation of cargo and recycling of macromolecules.

Furthermore, Gal-3 modulates TFEB (Transcription Factor EB), a master regulator of lysosomal biogenesis and autophagy  By influencing TFEB nuclear translocation, Gal-3 promotes the expression of lysosomal hydrolases and membrane proteins, thus optimizing lysosomal degradation capacity.

In the context of chemoresistance, Gal-3-mediated autophagy allows cancer cells to evade chemotherapy-induced apoptosis by degrading damaged organelles and proteins, promoting cellular survival and adaptation to stress [36]. This highlights Gal-3's potential as a therapeutic target in cancers where autophagy contributes to tumour progression and drug resistance.

### 3.3 Signal Transduction Pathways

Galectin-3 (Gal-3) plays a critical role in the modulation of key oncogenic signalling pathways.

One of the most well-documented pathways regulated by Gal-3 is the K-Ras-Raf-Erk1/2 signalling cascade, which is crucial for promoting migration and invasion in colorectal cancer cells . Gal-3 enhances the phosphorylation of Raf and MEK, leading to sustained activation of Erk1/2, which in turn promotes tumour aggressiveness. This interaction underscores the significance of Gal-3 in facilitating tumour progression. The intracellular functions of Galectin-3 span multiple oncogenic pathways that contribute to cancer progression and therapy resistance. Table 1 provides a summary of key intracellular roles of Galectin-3 in cancer cells.

Table 1. Intracellular Roles of Galectin-3 in Cancer Progression.

| Function | Mechanism of Galectin-3 | Implication in Cancer | References |
|---|---|---|---|
| Apoptosis Inhibition | Binds to Bcl-2, prevents Bax/Bak activation, and stabilizes mitochondrial integrity | Increases therapy resistance, allowing cancer cells to evade apoptosis | [31] |
| Autophagy Modulation | Interacts with LC3 and LAMP2 to regulate autophagosome formation | Enhances cell survival under metabolic stress and drug-induced toxicity | [37] |
| Wnt/β-catenin Signalling | Stabilizes β-catenin, promotes nuclear translocation | Drives cancer stemness, enhances invasion and metastasis | [7] [38] |
| PI3K/Akt Pathway Activation | Promotes phosphorylation of PI3K/Akt | Increases cell proliferation, reduces sensitivity to targeted therapy | [32] |
| Notch Signalling Activation | Stabilizes Notch1 intracellular domain | Supports cancer stem cell properties, contributes to tumour recurrence | [33] |
| mRNA Splicing Modulation | Interacts with spliceosome complexes | Alters gene expression patterns to Favor tumorigenesis | [39] |

Additionally, Gal-3 has been shown to stabilize the nuclear protein p21, a cyclin-dependent kinase inhibitor, which affects cell cycle progression and apoptosis in prostate cancer cells [40]. By stabilizing p21, Gal-3 prevents its proteasomal degradation, thereby contributing to cancer cell survival and proliferation.

Moreover, Gal-3's involvement in the PI3K/Akt signalling pathway is particularly noteworthy. Gal-3 can bind to PI3K and activate its downstream signalling cascade, promoting cell survival, proliferation, and metabolic adaptation [32]. In breast cancer, Gal-3 enhances the expression of HER2 and EGFR, which are key components of the PI3K/Akt pathway, thereby contributing to trastuzumab resistance [9] This resistance is a major therapeutic challenge in HER2-positive breast cancer, further emphasizing the role of Gal-3 in drug evasion mechanisms.

In addition to the PI3K/Akt pathway, the Notch signalling pathway is influenced by Gal-3. In stem cells for ovarian cancer, Gal-3 binds to the Notch1 intracellular domain, stabilizing its nuclear localization, which is essential for maintaining stemness and tumorigenic potential [33]. This suggests that Gal-3 not only promotes tumour growth but also supports cancer stem cell populations, contributing to metastasis and recurrence.

Gal-3 also regulates mRNA splicing within the nucleus, significantly impacting oncogenic signalling networks. It interacts with spliceosome complexes, affecting the expression of genes involved in cancer progression [39]. This suggests that Gal-3 modulates the transcriptome of cancer cells, influencing their behaviour and therapeutic response.

Furthermore, Gal-3 is thought to be involved in regulating integrin-linked kinase (ILK) signalling, which is crucial for cell adhesion and migration [41]. By influencing ILK signalling, Gal-3 can help cancer cells migrate and invade more easily, which can lead to metastasis.

## 4. Therapeutic Implications of Galectin-3 Targeting

### 4.1 Challenges in Targeting Galectin-3

Galectin-3 presents significant challenges for therapeutic targeting due to its multifunctionality and involvement in both intracellular and extracellular processes, complicating inhibitor design. Intracellularly, Gal-3 regulates signalling, apoptosis, and autophagy, while extracellularly, it facilitates adhesion, immune modulation, and tumour progression [42] [43]. The redundancy of galectin functions means targeting Gal-3 could inadvertently affect other pathways, leading to unintended consequences. For instance, inhibiting Gal-3 may reduce tumour growth but could also disrupt normal cellular functions or promote adverse effects.

The complexity of Gal-3's localization further complicates selective inhibition, as it functions in the cytoplasm, nucleus, and extracellular space [43]. Current research focuses on developing small-molecule inhibitors and monoclonal antibodies targeting Gal-3, with some undergoing preclinical testing for conditions like fibrosis and cancer [44]. However, further mechanistic studies are necessary to understand its activation and secretion, which could improve therapeutic strategies [42].

### 4.2 Current Therapeutic Strategies

Recent advancements in Galectin-3 inhibitors show promise, particularly in cancer therapy. Urolithin A, a metabolite of ellagic acid, exhibits antioxidant and anti-inflammatory properties and enhances cancer immunosurveillance by activating FOXO1, leading to CD8+ T cell expansion [45] However, no direct evidence confirms its role as a Galectin-3 inhibitor, warranting further research.

Other small-molecule inhibitors, such as GB1211, have undergone clinical trials, demonstrating safety and potential for enhancing cancer therapy GB1107 has shown efficacy in preclinical models by inhibiting lung adenocarcinoma growth and boosting immune checkpoint response [47]. TD139, in trials for pulmonary fibrosis, has shown therapeutic benefits in corneal neovascularization and fibrosis models [43].These inhibitors selectively target Galectin-3, potentially reducing tumour progression and improving patient outcomes.

### 4.3 Preliminary Results from Early Cancer Models

The early cancer models of Galectin-3 inhibitors have provided valuable insight into possible benefits and limitations. For example, studies illustrated that the inhibition of Galectin-3 by specific inhibitors, such as GB1211 and modified citrus pectin, suppresses anoikis resistance and invasive capacity in thyroid cancer cells, suggesting that targeting Galectin-3 may promote chemosensitivity and radiosensitivity [48]. In another study, the natural Galectin-3 inhibitor modified citrus pectin-induced cell cycle arrest and apoptosis in tumour cells, further supporting the therapeutic potential of Galectin-3 targeting [49].

However, it has remained a challenge to translate this finding from preclinical models to clinical applications. Whereas the first results seem promising, the effectiveness of inhibitors in human trials remains yet to be established. For instance, though GB1211 had been found to be safe within early-phase trials, its effectiveness in treating cancers of a specific type remains under investigation [47]. Moreover, multifunctionality complicates interpretation because the effects on other cellular pathways may result as a consequence of inhibiting Galectin-3

### 4.4 The Gap Between Preclinical Research and Clinical Applications

Despite the encouraging preclinical results, there is a notable gap between research findings and clinical applications. One significant challenge is the complexity of Galectin-3's role in various biological processes, which can lead to variability in patient responses to treatment. The redundancy of galectin functions means that targeting Galectin-3 could inadvertently affect other galectins or related pathways, complicating the therapeutic landscape [52].

Moreover, the clinical trials from the preclinical animal models sometimes reflect differences related to the drug metabolism, efficacy, and safety profiles. For instance, while some inhibitors have displayed potent activities in preclinical models, their translation into human subjects is not as promising because of differences in pharmacokinetics and pharmacodynamics [49].

### 5 Future Directions

Developing intracellular Galectin-3 inhibitors is crucial for targeting its oncogenic roles in apoptosis, autophagy, and signal transduction. Intracellular Gal-3 interacts directly with survival pathways, including Bcl-2 (apoptosis inhibition), LC3 (autophagy regulation), and β-catenin (Wnt signalling), making it a prime target for disrupting cancer cell survival.

A promising approach involves small-molecule inhibitors that block Gal-3's CRD domain, preventing interactions with pro-survival proteins. Selective inhibitors, as highlighted by [50] must differentiate Gal-3 from Gal-1 and Gal-7 to avoid functional competition. Additionally, mutational tuning of Gal-3 binding sites could enhance inhibitor specificity [51].

Combining Gal-3 inhibitors with immunotherapy, chemotherapy, or targeted therapy is another viable strategy. Gal-3 contributes to immune evasion by capturing interferon-gamma, reducing T-cell infiltration [53]. Inhibiting Gal-3 enhances chemotherapeutic sensitivity in breast and prostate cancers, potentially slowing tumour progression through synergy [54].

Personalized medicine approaches could optimize treatment by profiling Gal-3 levels in tumours, enabling tailored inhibitor-based therapies for patients with high Gal-3 expression, while others may benefit more from conventional treatments [55].

Galectin-3 also serves as a biomarker for cancer prognosis and early detection, as its overexpression in cancers such as lung and breast correlates with poor outcomes [55] [56]. Measuring serum or tissue Gal-3 levels may aid in early diagnosis, timely treatment, and improved survival rates.

## 6. Discussion

Galectin-3 plays a significant role in cancer by regulating intracellular pathways like apoptosis, autophagy, and oncogenic signalling (Wnt/β-catenin, PI3K/Akt, and Notch), while also promoting metastasis, immune evasion, and angiogenesis extracellularly [7, 25, 33, 41]. In this regard, its intracellular interactions, which include Bcl-2, LC3, and β-catenin, are associated with promoting tumour survival and therapy resistance [31, 37] With this role of intracellular Gal-3, it comes out as an attractive target for therapy, especially against resistance to therapy.

Current Gal-3 inhibitors mainly target its extracellular functions, with some molecules such as GB1211 and TD139 in clinical trials regarding their potential in metastasis reduction and enhancement of immune responses However, since intracellular Gal-3 is directly involved in the process of therapy resistance, targeting its interactions with Bcl-2, PI3K/Akt, and β-catenin would be a more direct way to sensitize tumours to chemotherapy and immunotherapy. This is particularly relevant for HER2-positive breast cancer, where Gal-3 contributes to trastuzumab resistance and for lung and colorectal cancers, where it enhances invasive potential through Wnt/β-catenin signalling. Moreover, Gal-3 expression varies across cancer types, being overexpressed in prostate, lung, and colorectal cancers but downregulated in certain subtypes of breast cancer, thus underlining the importance of biomarker-driven, personalized treatment approaches.

Despite its therapeutic promise, challenges remain in designing selective Gal-3 inhibitors that minimize off-target effects. The structural similarity of Gal-3 with other galectins restricts the development of highly specific inhibitors, which is a concern in terms of side effects on normal cellular functions [57] Besides, the redundancy in Gal-3 functions within various oncogenic pathways means that its inhibition must be carefully tailored to avoid disrupting essential physiological processes. This highlights the need for innovative approaches, including combining Gal-3 inhibitors with chemotherapy or immunotherapy to enhance treatment sensitivity and overcome resistance mechanisms [55]. Future research should focus on refining intracellular Gal-3 inhibitors, understanding its interactions at the molecular level, and developing personalized therapeutic strategies based on Gal-3 expression profiles in different tumour types. Overcoming these challenges will be crucial in translating Gal-3-targeted therapies into clinically effective cancer treatments.

## 7. CONCLUSION

Galectin-3 functions as a multifunctional protein that regulates cancer progression through apoptosis inhibition, autophagy modulation, and key oncogenic pathways, operating both intracellularly and extracellularly. Its role in immune evasion, metastasis, and therapy resistance highlights its potential as a promising therapeutic target and biomarker. However, a major challenge lies in developing highly specific inhibitors that selectively block its tumorigenic functions without disrupting its essential physiological roles.

Current research on Galectin-3 inhibitors, including small molecules and monoclonal antibodies, shows promise but requires further clinical validation. Combining Galectin-3 inhibitors with chemotherapy or immunotherapy could enhance treatment efficacy. Additionally, investigating its role in nuclear signalling and selective autophagy warrants deeper exploration to refine targeted therapeutic approaches.

Future studies should focus on the development of highly specific intracellular and extracellular inhibitors, validation of Gal-3 as a biomarker for early detection, and understanding its interactions in various types of cancer. Furthermore, integrating Galectin-3 targeting with immunotherapy, chemotherapy, and personalized medicine strategies could significantly improve patient outcomes. Addressing these gaps will be crucial in harnessing Galectin-3 for improved diagnostics and therapeutics in cancer.

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