Section A-Research paper

Overview about Role of Galectin-3 in Different Rheumatological Diseases

Mirvat Abdelhamid Eltoukhy[1], Esraa Mohsen Elsayed [1], Marwa Mohammed Esawy[2], Amany Mohammed Ebaid [1].

1- Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University
2- Clinical Pathology Department, Faculty of Medicine, Zagazig University
Email: es.moh94918@gmail.com

Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

Abstract

Background: Galectins are a class of proteins that bind specifically to β-galactoside sugars, such as *N*-acetyllactosamine which can be bound to proteins by either N-linked or O-linked glycosylation. They are also termed S-type lectins due to their dependency on disulphide bonds for stability and carbohydrate binding. Mammalian galectins have either one or two highly conserved carbohydrate recognition domains (CRDs) to form complexes that crosslink glycosylated ligands. Gal-3 is important in numerous biological activities in various organs, including cell proliferation, apoptotic regulation, inflammation, fibrosis, and host defense. The presence of Gal-3 has been demonstrated also in the tissues of the lungs, spleen, stomach, and also in the heart, kidneys, pancreas, and liver. Thus, a significant increase of Gal-3 level in the blood serum is observed in many pathological processes which take place in various tissues. Gal-3 affects differentiation and growth of various immune cells: it induces apoptosis in T cells and neutrophils; and it activates several lymphoid and myeloid cells resulting in mediator release, superoxide anion production, and cytokine production. Notably, Gal-3 induces monocyte–macrophage differentiation, interferes with dendritic cell fate decision, regulates apoptosis on T lymphocytes and inhibits B-lymphocyte differentiation into immunoglobulin secreting plasma cells. Considering the influence of these cell populations in the pathogenesis of several autoimmune diseases, Gal-3 seems to play a role in development of autoimmunity. Many studies have revealed that Gal-3 plays an important role as a diagnostic or prognostic biomarker for certain types of heart disease, kidney disease, viral infection, autoimmune disease, neurodegenerative disorders, and tumor formation. In particular for detecting many of these diseases in their early stages.

Keywords: Galectin-3, rheumatology

Introduction

Galectins are a class of proteins that bind specifically to β-galactoside sugars, such as *N*-acetyllactosamine which can be bound to proteins by either N-linked or O-linked glycosylation. They are also termed S-type lectins due to their dependency on disulphide bonds for stability and carbohydrate binding. Mammalian galectins have either one or two highly conserved carbohydrate recognition domains (CRDs) to form complexes that crosslink glycosylated ligands (**Dings et al ., 2018).**

Lectins are carbohydrate-binding proteins that are highly specific for sugar groups that are part of other molecules, so cause agglutination of particular cells or precipitation of glycoconjugates and polysaccharides**(Chen et al., 2014).**

Galectins have been classified into three subgroups according to their CRD number and function (**Figure 1**):

(1) Proto-type galectins (galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15), containing a single CRD that form non-covalent homodimers.

(2) tandem-repeat galectins (galectin-4, -6, -8, -9, and -12), carrying two CRD motifs connected by a peptide linker.

(3) chimera-type galectin (galectin-3), which are characterized by having a single CRD and an amino-terminal polypeptide tail region.

All members of galectin family were numbered consecutively by order of discovery **(Johannes et al ., 2018).**

Many galectins are either bivalent or multivalent with regard to their carbohydrate-binding activities: one-CRD galectins often exist as dimers; galectin-3 forms petamers upon binding to multivalent carbohydrates; and two-CRD galectins have two carbohydrate-binding sites. Thus, galectins can form lattices with multivalent glycoconjugates **(Brinchmann et al .,2018).**

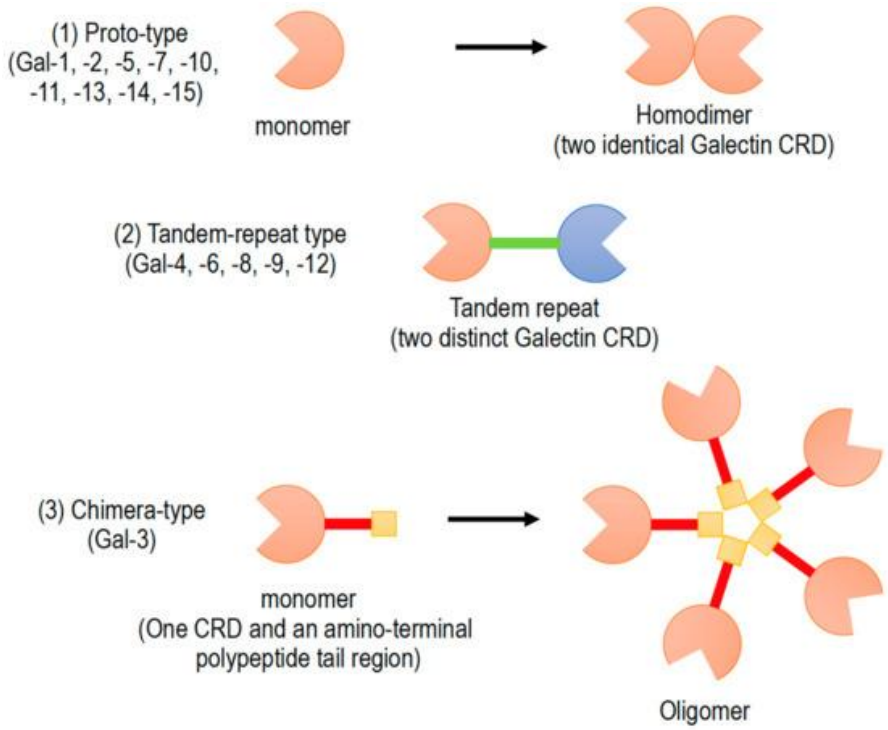

Figure 1. Schematic diagram of galectin family members. Galectin members are divided into three types based on the organization of galectin carbohydrate recognition domain (CRD) **(Hara et al .,2020).**

Galectins function:

Galectins play important roles in cell-to-cell and cell-to-matrix interactions by binding to endogenous glycans. Galectin signaling can regulate cellular functions at the cell surface. Biological functions of galectins, which are not yet fully understood, include roles in development, tissue regeneration, regulation of immune cell activities, and other important cellular functions **(Brinchmann et al .,2018).**

Galectins are important regulators of inflammatory responses and immune system. In fact, galectins are expressed in many inflammatory cells, such as macrophages. Depending on the inflammatory environment, galectins promote pro-inflammatory or anti-inflammatory responses. The galectin-mediated specific molecular recognition of glycans on the cell surface have revealed their roles as innate immune functions against potential pathogens and parasites. As a part of the innate immune system for microbial recognition/effector functions, galectins bind to exogenously exposed glycans on the surface of viruses, bacteria, fungi, and parasites **(Chen et al., 2014).**

Galectin-3(Gal-3)

- ***structure;***

Gal-3 is the most studied member of the galectin family. It is the sole member of chimera-type family of galectins. Its structure consists of two domains, the C-terminal CRD, with highly conserved residues

between members of the family, and the N-terminal domain, with a unique short end continuing into an intervening proline-glycine-alanine- tyrosine-rich repeat motif **(Pugliese et al .,2015).**

The N-terminal domain contains sites for phosphorylation and other determinants important for the secretion of the lectin by a novel, nonclassical mechanism. The C-terminus is the CRD, consisting of about 135 amino acid residues; this is what defines the molecule as a galectin **(Farhadi et al ., 2021).**

Gal-3 is encoded by the *LGALS3* Gene, The structure of the *LGALS3* gene is consistent with the multi-domain organization of the protein. The gene for Gal-3 is composed of six exons and five introns (human locus 14q21-22). (**Dings et al ., 2018).**

Gal-3, like most members of the galectin family, acts as a receptor for ligands containing poly-*N*-acetyllactosamine sequences which consist of many disaccharide units. However, Gal-3 appears to have an increased affinity for the more complex oligosaccharides **(Brinchmann et al ., 2018).**

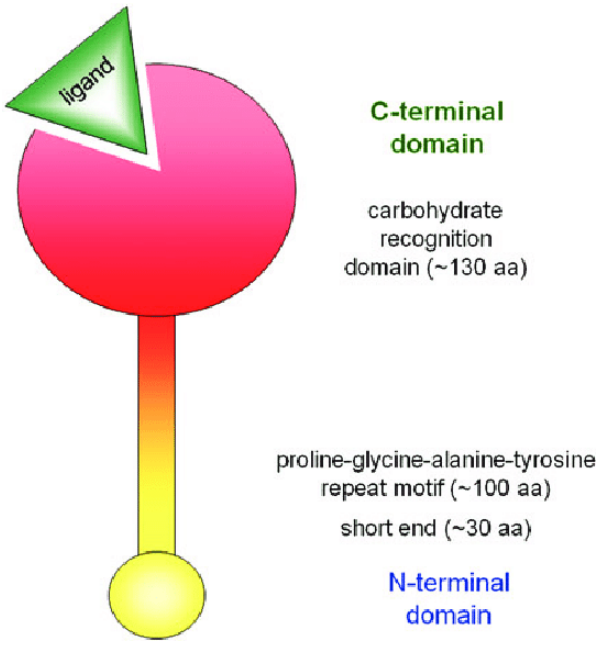

Figure 2. Galectin-3 structure. Aa, aminoacids **(Pugliese et al ., 2015).**

- ***Subcellular Localization;***

Although Gal-3 is predominantly located in the cytoplasm, it has also been detected in the nucleus, on the cell surface and in the extracellular environment, suggesting a multifunctionality of this molecule **(Pugliese et al ., 2015).**

Extracellular Gal-3 modulates important interactions between epithelial cells and extracellular matrix, and plays a role in the embryonic development of collecting ducts . In contrast, intracellular Gal-3 is important for cell survival due to its ability to block the intrinsic apoptotic pathway . In this regard, it has been demonstrated that cytoplasmic Gal-3 in cancer cells is usually associated with an aggressive phenotype, in opposition to nuclear Gal-3 **(Gilson et al ., 2019).**

Nuclear localization of Gal-3 was first described in in vitro proliferating fibroblasts ,but not in fibroblasts with replicative deficiencies .Nuclear Gal-3 is localized mainly in interchromatin spaces and at the periphery of the fibrillar centers of nucleoli (**Chan et al ., 2018).**

secretion;

Gal-3 is synthesized on free ribosomes in the cytoplasm and lacks any signal sequence for translocation into the endoplasmic reticulum (ER). This protein has been shown to be secreted from cells by a novel, incompletely understood mechanism called ectocytosis, which is independent of the classical secretory pathway through the ER and Golgi system(**Dings et al ., 2018).**

- ***Role of Gal-3 in Different Clinical Conditions and Rheumatological Diseases***;

Gal-3 is important in numerous biological activities in various organs, including cell proliferation, apoptotic regulation, inflammation, fibrosis, and host defense **(Wang et al ., 2019).**

The presence of Gal-3 has been demonstrated also in the tissues of the lungs, spleen, stomach, and also in the heart, kidneys, pancreas, and liver. Thus, a significant increase of Gal-3 level in the blood serum is observed in many pathological processes which take place in various tissues **(Imran et al ., 2017).**

Many studies have revealed that Gal-3 plays an important role as a diagnostic or prognostic biomarker for certain types of heart disease, kidney disease, viral infection, autoimmune disease, neurodegenerative disorders, and tumor formation. In particular for detecting many of these diseases in their early stages **(Asleh et al .,2019).**

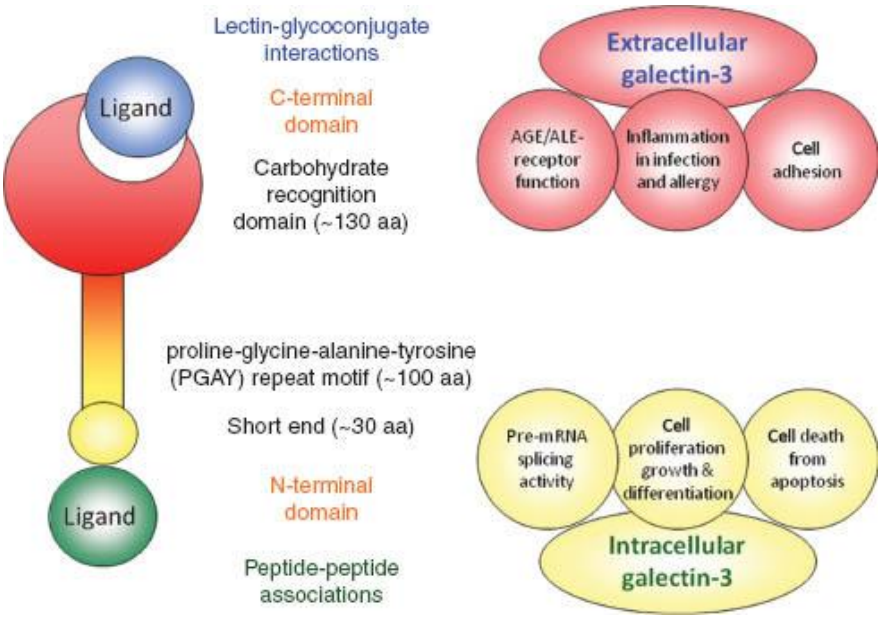

Figure 3. Schematic structure of galectin-3 and the intracellular and extracellular functions. aa, aminoacids; AGE, advanced glycation endproduct; ALE, advanced lipoxidation endproduct **(Pugliese et al ., 2014).**

1- Galectin-3 in immune and inflammatory responses;

Certain cells produce and secrete a large amount of Gal-3 as a response to various inflammatory stimuli. When secreted or externalized, Gal-3 may affect inflammatory cells by an autocrine or paracrine mechanism; it triggers/promotes respiratory burst in neutrophils and monocytes, it promotes adhesion of human neutrophils to laminin and endothelial cells, and acts as a chemoattractant for monocytes and macrophages **(Soares et al ., 2021).**

Gal-3 affects differentiation and growth of various immune cells: it induces apoptosis in T cells and neutrophils; and it activates several lymphoid and myeloid cells resulting in mediator release, superoxide anion production, and cytokine production **(Snarr et al ., 2020).**

Recombinant Gal-3 can also function like a chemokine in inducing migration of human monocytes and macrophages. Similar to chemokines, the activity is mediated through a pertussis toxin (PTX)-sensitive (G-proteincoupled) pathway and associated with a Ca2þ influx, and thus a specific chemokine receptor(s) may be involved**(Hara et al ., 2020).**

Gal-3 can also exert a suppressive effect on myeloid cells by inhibition of IL-5 production in human eosinophils . The fact that this lectin has promoting functions in some cells but suppressive activities in others may not be too surprising, since conceivably it can bind to either receptors that deliver positive signals or those that deliver negative signals (**Dings et al ., 2018).**

The importance of Gal-3 in inflammatory response also emerges from the property of Gal-3 to recognize galactoside-containing glycoconjugates on pathogens**(Soares et al ., 2021).**

In summary, Gal-3 can be positive and negative regulator of inflammatory response, depending on multiple factors, such as specific inflammatory conditions, the type of targeted cell or its expression level **(Blanda et al ., 2020).**

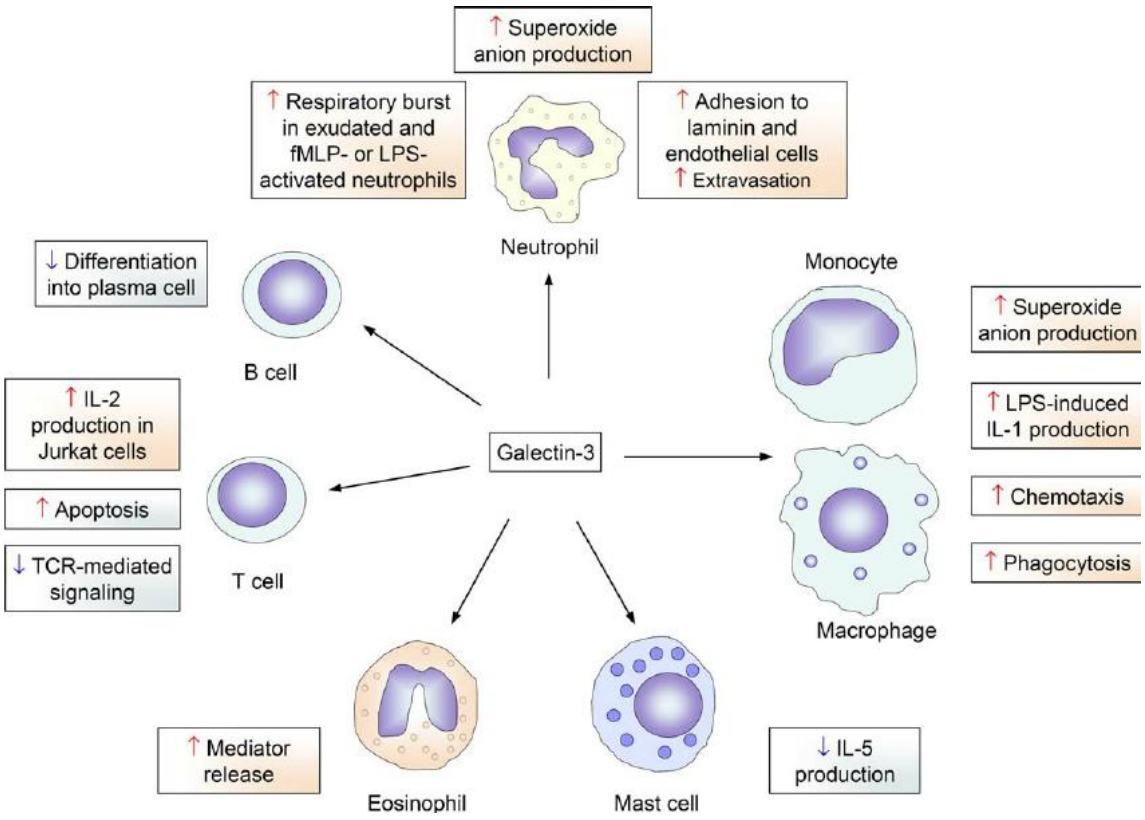

Figure 4. The effects of galectin-3 on immune cells. Red upwards arrows indicate positive effects, blue downwards arrows indicate negative effects. Pro-inflammatory effects of galectin-3 are indicated in red shaded boxes, anti-inflammatory effects are indicated in blue shaded boxes. fMLP — formyl-methionyl-leucyl-phenylalanine IL-1, -2, -5 — interleukin-1, -2, -5, LPS — lipopolysaccharide, TCR — T cell receptor **(Dong et al ., 2018).**

2- Galectin-3 in Rheumatoid Arthritis

In RA, the inflammatory process is mediated by activated monocytes (secreting IL-1b, IL-6, IL-7 and tumor necrosis factor-alpha (TNF)-a), fibroblast-like synoviocytes (FLS) and dysregulated osteoclasts (due to high levels of TNF-a and IL-17) . Activated T helper cells comprise a large proportion of the inflammatory cells that invade the synovial tissue and may therefore be a cell type of pathogenic importance **(Zhao et al ., 2021).**

Galectin 3 has been suggested to be a proinflammatory mediator since this lectin induces the production of reactive oxygen species (ROS) in human neutrophils and promotes chemotaxis in monocytes. The interaction of galectin 3 with T cells induces antiapoptotic activity, a phenomenon often correlated with a prolonged inflammatory response (**Salamanna et al .,2019).**

In addition to immune cells, FLS in the synovium of RA patients also express galectin-3 at high levels . While floating FLS only express low levels of galectin-3 , adhesion of FLS to cartilage components through CD51/CD61 induces galectin-3 expression (**Issa et al ., 2015).**

The increased numbers of adhering FLS contribute to the elevated galectin-3 levels in the RA synovium . Moreover, galectin-3 can induce rheumatoid FLS to secret a set of pro-inflammatory cytokines and chemokines including IL-6, granulocyte-macrophage colony-stimulating factor (GMCSF), TNF, CCL2, CCL3, and CCL5. The induction of cytokines and chemokines by galectin-3 appears to involve different signaling pathways(**Hu et al .,2017).**

In human patients, galectin-3 was detected in the synovial tissue of RA and JIA patients, with clear accumulation at the sites of cartilage invasion (**Issa et al .,2015).**

3- Galectin-3 in Ankylosing Spondylitis

Although the pathogenesis of AS is still unclear, there are several explanations for the role of galectin- 3 in AS . First, the Galectin-3 may regulate inflammatory responses in immune cells, and Galectin-3 as a pro-inflammatory cytokine accelerates the release of tumor necrosis factor-α and interleukin-6 **(Chen et al., 2015).** Second, Galectin-3 can activate myo-fibroblasts and promote fibrosis, it can promote inflammatory cytokine secretion in tissue fibroblasts, and considered as a critical mediator of transforming growth factor-β induced pulmonary fibrosis **(Slack et al., 2021).** Third, Galectin-3 gene expression is increased in inflammatory tissues in patients with juvenile idiopathic arthritis and the gene expressions of Galectin-3 are elevated in immune cell in systemic lupus erythematosus patients **(Peretz et al., 2021)**. Therefore, inflammation and immune dysfunction may increase serum Galectin-3 levels in patients with AS, and these pathological changes corporately contribute to the progression of disease in AS patients.

4- Galectin-3 in other rheumatic diseases

The serum concentration of Gal-3 is associated with skin fibrosis, proliferative vasculopathy and inflammation in systemic sclerosis, which is characterized by progressive fibrosis of the skin and certain internal organs, and may be a prominent biomarker of disease activity **(Koca et al .,2014).**

Gal-3 is involved in the inflammatory process of systemic lupus erythematosus (SLE).the glomerular expressions of Gal-3 were found to be higher in patients with SLE nephritis than in healthy controls, and its expression scores were found to correlate with serological activity markers and histological activity indices **(Gruszewska et al ., 2020).**

Gal-3 has been reported to be expressed and secreted by inflamed synovium in patients of osteoarthritis and Juvenile idiopathic arthritis . Gal-3 upregulation in the synovial tissues was suggested to be the cause of the defective mononuclear apoptosis observed in synovial inflammatory infiltrates from these patients **(Hara et al .,2020).**

5-Galectin-3 in other diseases

A correlation between galectin-3 expression levels and various types of fibrosis has been found. Galectin-3 is upregulated in cases of liver fibrosis, renal fibrosis, and idiopathic pulmonary fibrosis (IPF) **(Sciacchitano et al., 2018).**

Gal-3 has already been used as a novel biomarker in the early detection of myocardial dysfunction and heart failure . Gal-3 has been validated as a biomarker of fibrotic degeneration in acute myocarditis following cardiac viral infection. Also it is expressed in foam cells and macrophages in atherosclerotic lesions and may participate in the development of atherosclerosis**(Imran et al ., 2017).**

Gal-3 displays pathological expression in many tumors, such as in thyroid, pancreatic, and colon cancers Abnormal expression of tumor-associated galectins correlates with the development, progression and clinical aggressiveness of the tumors, as well as the contribution to metastatic phenotype. **(Kaltner et al ., 2017).**

Gal-3 appears to be a potent activator of fibroblasts in the kidneys . However, its absence is protective against renal myofibroblast accumulation and activation . Many studies, performed on mouse models of diabetic nephropathy and acute renal failure, concordantly indicate that Gal-3 is upregulated in such conditions (**Drechsler et al ., 2015).**

It was reported that Gal-3 is also associated with neurodegenerative diseases such as multiple sclerosis, Huntington's disease and Parkinson's disease,also the levels of Gal-3 have been reported to increase in ischemic brain damage**(Hara et al ., 2020).**

References

Asleh R., Enriquez-Sarano M., Jaffe A., et al ., (2019). Galectin-3 levels and outcomes after myocardial infarction: a population-based study. Journal of the American College of Cardiology, 73(18), 2286-2295.

Blanda V., Bracale U., Di Taranto et al .,(2020). Galectin-3 in cardiovascular diseases. International Journal of Molecular Sciences, 21(23), 9232.

Brinchmann M., Patel D., and Iversen M. (2018). The role of galectins as modulators of metabolism and inflammation. Mediators of inflammation, 2018.

Chan Y., Lin H., Tu Z., et al ., (2018). Dissecting the structure–activity relationship of galectin–ligand interactions. International journal of molecular sciences, 19(2), 392.

Chen H ., Weng I ., Hong M , et al., (2014); Galectins as bacterial sensors in the host innate response. Current opinion in microbiology, 17, 75-81.

Chen S., Sun, L., Brickner H., et al ., (2015). Downregulating galectin-3 inhibits proinflammatory cytokine production by human monocyte-derived dendritic cells via RNA interference. Cellular Immunology, 294(1), 44–53.

Dings R., Miller M., Griffin R., et al ., (2018). Galectins as molecular targets for therapeutic intervention. International journal of molecular sciences, 19(3), 905.

Dong R., Zhang M., Hu Q., et al ., (2018). Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy. International journal of molecular medicine, 41(2), 599-614.

Drechsler C., Delgado G., Wanner C., et al .,(2015). Galectin-3, renal function, and clinical outcomes: results from the LURIC and 4D studies. Journal of the American Society of Nephrology, 26(9), 2213-2221.

Farhadi S., Liu R., Becker M. et al ., (2021). Physical tuning of galectin-3 signaling. Proceedings of the National Academy of Sciences, 118(19), e2024117118.

Gilson R, Gunasinghe S, Johannes L., et al ., (2019). Galectin-3 modulation of T-cell activation: mechanisms of membrane remodeling. Progress in Lipid Research , 76 , 101010 .

Gruszewska E., Cylwik B., Gińdzieńska-Sieśkiewicz E., et al .,(2020). Diagnostic power of galectin-3 in rheumatic diseases. Journal of clinical medicine, 9(10), 3312.

Hara A., Niwa M., Noguchi K., et al., (2020). Galectin-3 as a next generation biomarker for detecting early stage of various diseases. Biomolecules , 10 (3), 389

Hu Y., Yéléhé-Okouma M., Ea H., et al ., (2017). Galectin-3: A key player in arthritis. Joint Bone Spine, 84(1), 15-20.

Imran T., Shin H., Mathenge N., et al ., (2017). Meta-analysis of the usefulness of plasma galectin-3 to predict the risk of mortality in patients with heart failure and in the general population. The American Journal of Cardiology, 119(1), 57-64.

Issa S., Christensen A., Lottenburger T., et al .,(2015). Within-day variation and influence of physical exercise on circulating Galectin- 3 in patients with rheumatoid arthritis and healthy individuals. Scandinavian journal of immunology, 82(1), 70-75.

Johannes L., Jacob R., and Leffler H. (2018). Galectins at a glance. Journal of cell science, 131(9), jcs208884

Kaltner H., Toegel S., Caballero G et al ., (2017). Galectins: their network and roles in immunity/tumor growth control. Histochemistry and cell biology, 147, 239-256.

Koca S., Akbas F., Ozgen M., et al ., (2014). Serum galectin-3 level in systemic sclerosis. Clinical rheumatology, 33, 215-220.

Peretz A., Rasmussen N., Jacobsen S., et al ., (2021). Galectin-3-binding protein is a novel predictor of venous thromboembolism in systemic lupus erythematosus. Clin Exp Rheumatol, 39(6), 1360–1368.

Pugliese G., Iacobini C., Pesce C. et al ., (2015). Galectin-3: an emerging all-out player in metabolic disorders and their complications. Glycobiology, 25(2), 136-150.

Pugliese G., Iacobini C., Ricci C., et al ., (2014). Galectin-3 in diabetic patients. Clinical Chemistry and Laboratory Medicine (CCLM) , 52 (10), 1413-1423.

Salamanna F., Veronesi F., Frizziero A., et al ., (2019). Role and translational implication of galectins in arthritis pathophysiology and treatment: A systematic literature review. Journal of Cellular Physiology, 234(2), 1588-1605.

Sciacchitano S., Lavra L., Morgante A., et al., (2018). Galectin-3: one molecule for an alphabet of diseases, from A to Z. International journal of molecular sciences, 19(2), 379

Slack R., Mills R., & Mackinnon, A (2021). The therapeutic potential of galectin-3 inhibition in fibrotic disease. The International Journal of Biochemistry & Cell Biology, 130, 105881.

Snarr B., St-Pierre G., Ralph B., et al ., (2020). Galectin-3 enhances neutrophil motility and extravasation into the airways during Aspergillus fumigatus infection. PLoS Pathogens, 16(8), e1008741.

Soares L., Al-Dalahmah O., Hillis J., et al ., (2021). Novel galectin-3 roles in neurogenesis, inflammation and neurological diseases. Cells, 10(11), 3047.

Wang C., Zhou X., Ma, et al ., (2019). Galectin-3 may serve as a marker for poor prognosis in colorectal cancer: A meta-analysis. Pathology-Research and Practice, 215(10), 152612.

Zhao J., Guo S., Schrodi S., et al ., (2021). Molecular and cellular heterogeneity in rheumatoid arthritis: mechanisms and clinical implications. Frontiers in Immunology, 12, 790122.