Galectin-3 and Inflammation

Lei Wan1–3 and Fu-Tong Liu4,5

1 School of Chinese Medicine, China Medical University, Taichung, Taiwan. 2 Department of Biotechnology, Asia University, Taichung, Taiwan. 3 Department of Gynecology, China Medical University Hospital, Taichung, Taiwan. 4 Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. 5 Department of Dermatology, University of California Davis School of Medicine, Sacramento, CA, USA.

ABSTRACT: Galectins are a family of β-galactoside-binding proteins that share a consensus sequence in the carbohydrate recognition domain (CRD). Galectin-3 is the most widely studied family member and can be found in the cellular cytoplasm and nucleus, as well as extracellularly in various tissues. The 30-kDa molecule contains an N-terminal proline-rich domain that is important for its oligomerization and a C-terminal CRD for carbohydrate-binding activity. Many studies have shown that galectin-3 may regulate inflammation through a variety of mechanisms. Endogenous galectin-3 has been shown to be involved in the pathogenesis of various diseases, such as fibrosis in the lung, liver, and heart, diabetes mellitus, coronary artery disease, and allergic diseases. In this review, we briefly discuss the pro- or anti-inflammatory roles, as well as potential clinical implications of galectin-3 in these disorders.

KEYWORDS: galectin-3, inflammation, fibrosis, diabetes mellitus, coronary artery disease, allergic disease

Introduction

Galectins are a family of galactoside-binding proteins that share a consensus sequence in the carbohydrate recognition domain (CRD). Till date, seventeen mammalian galectins have been identified, a majority of which contains a single CRD (1-CRD) whereas others have two distinct but homologous CRDs (2-CRD). Galectin-3 is unique in that it contains one CRD and a nonlectin domain composed of proline- and glycine-rich short tandem repeats. Some galectins are widely expressed in different tissues, whereas others are more tissue specific. Galectin family members differ in their carbohydrate-binding specificity and affinity.1–2 The 1-CRD and 2-CRD galectins can homodimerize or heterodimerize. Thus, almost all galectins exert bivalent or oligovalent carbohydrate-binding activities.

Galectins contain no classical localization signal sequence and exist as intracellular proteins. Although they can be detected on the cell surface and in the extracellular space,3–5 it remains unknown how these proteins are transported to these areas. Galectins do not have specific cell surface receptors but bind to various glycoproteins via their carbohydrate moieties. Recombinant galectins exhibit various in vitro activities by interacting with cell surface glycoproteins or extracellular matrix proteins in a carbohydrate-dependent manner. Additionally, many studies have demonstrated intracellular biological activities for galectins, some of which are independent of carbohydrate binding. Indeed, galectins bind to several intracellular signaling molecules to regulate signal transduction.1,2 Galectins have been shown to participate in cell adhesion, migration, and growth. They can also influence the activation and regulation of both innate and adaptive immune responses, which is most relevant to the focus of this review. Importantly, they have been implicated in the pathogenesis of a variety of diseases, including cancer initiation, progression, and metastasis.

Galectin-3 is the most widely studied family member and can be found in the cellular cytoplasm and nucleus, as well as extracellularly in various tissues.4–6 The 30-kDa molecule contains an N-terminal proline-rich domain that is important for its oligomerization and a C-terminal CRD. Oligomerization occurs in the presence of multivalent glycans.7 Accordingly, glycans binding through its C-terminal CRD elicits protein oligomerization via its N-terminal domain.8 Galectin-3 oligomerization is implicated in various biological activities of the protein and is associated with its ability to cluster or form lattices with cell surface glycoconjugates and mediate cell–cell interactions.9 Galectin-3 is found in macrophages, monocytes, dendritic cells, eosinophils, mast cells, nature killer cells, and T- and B-cells. Differences in cell type, external stimuli, and environmental conditions may alter the expression level of galectin-3.10 Galectin-3 is a differentiation marker for human monocytes or promyelocytic cell line HL-60, which can be differentiated into macrophage-like cells by phorbol ester treatment.11 Galectin-3 is considered as macrophage activation marker as it is overexpressed in phagocytic macrophages.12 Galectin-3 level is also increased...
in myelin-activated microglia and macrophages. Conversely, activation of human monocytes by lipopolysaccharide and interferon-γ suppressed galectin-3 expression. THP-1 cells treated with nonsteroidal or corticosteroidal anti-inflammatory drugs showed a lowered expression level of galectin-3. The expression levels of galectin-3 are low or undetectable in resting B- and T-cells, but upregulated when these cells are activated.

The biological activities of galectin-3 which vary in different cells and tissues are as follows: (1) Extracellular galectin-3 binds to cell surface and extracellular matrix glycans to alter diverse physiologic and pathologic processes, such as apoptosis, migration, adhesion, angiogenesis, and inflammatory responses. (2) Galectin-3 exhibits high sequence similarity with Bcl-2, which is known for its antiapoptosis properties, and binds to Bcl-2. (3) T-leukemia cells transfected with galectin-3 has lower apoptosis rate; thus, galectin-3 may be antiapoptotic through its Bcl-2-like activities or interaction with Bcl-2. (4) Overexpression of galectin-3 in human breast cancer cell line inhibits apoptosis induced by cisplatin without affecting the expression levels of Bcl-2, Bcl-XL, or Bax. (5) Extracellular galectin-3 enhances the adhesion between neutrophils and laminin and activate monocytes. (6) Exogenous galectin-3 enhances endothelial cell capillary tube formation to promote angiogenesis.

Many studies have shown that galectin-3 may regulate inflammation through a variety of mechanisms. The majority of the studies used recombinant protein to demonstrate extracellular actions of the protein on a variety of cells. The functions of endogenous galectin-3 with regard to its roles in inflammation are focused in this review.

The Role of Galectin-3 in Fibrosis

Pulmonary fibrosis. Pulmonary fibrosis results from inflammation and tissue remodeling that occurs after lung tissue injury, and it is characterized by the proliferation, differentiation, and activation of pneumocytes, alveolar macrophages, capillary endothelial cells, and myofibroblasts. However, increased galectin-3 expression is detected in alveolar macrophages as well as in type I and type II alveolar epithelial cells in a rat model of irradiation-induced lung inflammation and repair. Galectin-3 knockout mice also exhibited a marked reduction in transforming growth factor β1 (TGF-β1) secretion and bleomycin-induced lung fibrosis. Additionally, these mice expressed lower levels of collagen I, α-smooth muscle actin (α-SMA), and vimentin, resulting in attenuated epithelial–mesenchymal transition in response to TGF-β1 stimulation. Moreover, β-catenin activation by TGF-β1 and bleomycin-induced lung fibrosis was notably lower in galectin-3-deficient cells and in the presence of the galectin-3 inhibitor TD139, a high-affinity inhibitor binding to CRD of galectin-3 (Kᵢ = 14 nM).

Hermansky–Pudlak syndrome (HPS) is an autosomal recessive disorder characterized by oculoctaneous albinism. Some HPS patients develop pulmonary fibrosis (HPSPF), particularly those carrying HPS-1 gene mutations. Importantly, bronchoalveolar lavage (BAL) fluids and lung biopsies from patients with HPSPF were also found to contain higher amounts of galectin-3. HPS-1 gene mutation has been shown to impair intracellular trafficking of galectin-3 to the plasma membrane, which may further cause a defect in lysosomal degradation of galectin-3. Restoring the expression level of HPS-1 gene in HPS-1 mutated lung fibroblasts normalized the galectin-3 expression level.

Chronic asthma may lead to airway remodeling characterized by subepithelial fibrosis, increased smooth muscle mass, increased mucus secretion, neovascularization, and airway edema and narrowing. In a 12-week chronic allergic airway inflammation model with repetitive allergen challenges, galectin-3 knockout mice exhibited significantly less subepithelial fibrosis, smooth muscle thickness, mucus secretion, and neovascularization in the lung. There were increased expression levels of galectin-3 in the BAL fluid and lung tissue. Moreover, the number of eosinophils and the expression levels of eotaxin-1, interleukin (IL)-5, and IL-13 were markedly lower in the BAL fluid and lung tissue of galectin-3 knockout mice when compared with wild-type controls. Additionally, galectin-3 knockout mice also expressed much lower amounts of TGF-β, an important cytokine for promoting tissue remodeling.

Liver fibrosis. Liver fibrosis is a common result of chronic inflammatory tissue injury caused by toxic chemicals, hepatitis virus infection, alcoholic/nonalcoholic steatosis, and immune system-mediated injury. Fibroblasts and myofibroblasts are important in the initiation and progression of scar formation in tissues.

Galectin-3 expression levels are increased in patients with liver fibrosis caused by autoimmune disease, copper or iron overload, alcoholic steatosis, or primary biliary cirrhosis. In a CCL4-induced rat liver cirrhosis animal model, galectin-3 expression was elevated in the liver and correlated with disease onset and progression. Collagen I and α-SMA expression levels reduced in galectin-3 knockout mouse liver. Notably, CCL4-induced myofibroblast activation in the liver was galectin-3 dependent. Moreover, bone marrow reconstitutions in CCL4-treated male mice significantly reduced galectin-3 expression in liver, but had no significant effect on TGF-β expression, emphasizing the importance of galectin-3 in the pathogenesis of CCL4-induced liver fibrosis. The necessity of galectin-3 in the pathogenesis of liver fibrosis has also been demonstrated in a thioacetamide–induced animal model. Consistently, thioacetamide-induced liver fibrosis was improved in mice treated with two galectin-3 inhibitors, GM-CT-01 (galactomannan) and GR-MD-02 (galactoarabino-rhamnogalaturonan). GM-CT-01 and GR-MD-02 have been reported to bind to galectin-3 with the affinity of 2.8 and 2.9 μM, respectively, and to galectin-1 with the affinity of 10 and 8 μM, respectively. Whether the effects of these compounds are indeed
due to their targeting of galectin-3 (or galectin-1) has not been established. Galectin-3 was also found in the pathogenesis of nonalcoholic steatohepatitis (NASH). In a NASH model induced by atherogenic diet, galectin-3 knockout mice exhibited significantly less steatosis compared with wild-type mice. NASH was detected in all wild-type mice but found only in 30% galectin-3 knockout mice, and the latter showed less inflammation, degeneration, and fibrosis. The effects correlated with reduced accumulation of advanced lipoxidation end products.41

Cardiac fibrosis. Heart failure is a significant clinical problem associated with high morbidity and mortality. Heart failure generally develops in a slow and silent manner. During this process, cardiac remodeling is progressively ongoing and eventually leads to symptomatic cardiac diseases. Cardiac remodeling is characterized by the changes in extracellular cardiac matrix proteins, such as collagen.

Increased serum galectin-3 levels have been detected in patients with heart failure, where it is considered to be a potential diagnostic and prognostic marker. A study of 7,968 subjects revealed that serum galectin-3 was associated with several cardiovascular disease risk factors, including blood pressure, serum cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, creatinine, urinary albumin excretion rate, C-reactive protein, and N-terminal pro-B-type natriuretic peptide. Moreover, galectin-3 levels were higher in females and showed a stronger association with cardiac risk factors.42 Significantly, patients with serum galectin-3 concentrations >30 ng/mL had a greater likelihood of heart failure-associated hospitalization or death.43 Ho et al also measured serum galectin-3 concentrations in 3,353 subjects and confirmed these results. Increasing left ventricular mass was also associated with sera galectin-3 levels (P = 0.001). This study found that galectin-3 expression levels increased the risk of heart failure by 1.28-fold and was also associated with all-cause mortality (hazard ratio = 1.15).44 In a study of the elderly (232 patients; mean age 71 ± 10 years), serum galectin-3 levels were significantly associated with mortality after adjustment for age and gender and found to be a reliable predictor of heart failure.45

Obesity increases leptin secretion, which is known to affect cardiac function and promote cardiac fibrosis.46,47 Notably, male rats fed with a high-fat diet for six weeks exhibited cardiac hypertrophy and fibrosis with an associated increase in leptin, collagen I, galectin-3, and TGF-β expression in the heart tissue. Galectin-3 inhibition by N-acetylglucosamine reduced leptin-induced collagen I secretion in cardiac fibroblasts, suggesting that the increase in leptin during obesity can lead to cardiac fibrosis, which can be partially inhibited by limiting galectin-3 activity.48 Similar results were found in an aldosterone-induced vascular fibrosis animal model demonstrating that aldosterone-induced vascular fibrosis was characterized by increased galectin-3 and collagen I expression in vascular smooth muscle cells and aorta. This form of vascular fibrosis was suppressed in galectin-3 knockout mice or mice treated with citrus pectin, a galectin-3 inhibitor.49 However, whether this is indeed due to inhibiting galectin-3 is not clear, as the specificity of citrus pectin has not been established. In addition, galectin-3 may exert its effect by functioning intracellularly, and this inhibitor may not be able to get inside the cells.

Infection with the protozoan Trypanosoma cruzi can lead to a chronic heart condition known as Chagas disease, which can cause severe cardiomyopathy and cardiac fibrosis. In a mouse model of T. cruzi infection, myocarditis was associated with an increased expression of collagen I, α-SMA, galectin-3, and interferon-γ in the heart;50 these were reduced in galectin-3 knockout mice (Fig. 1).51

Galectin-3 in Metabolic Disease Pathogenesis

Obesity is a common risk factor for metabolic syndrome, a group of several diseases that include insulin resistance,
hypertension, glucose intolerance and toxicity, hepatic steatosis, atherogenic dyslipidemia, and type 2 diabetes mellitus (DM).\(^{32-35}\) Obesity-associated insulin resistance is a major risk factor for the development of type 2 DM, which involves multiple organs, such as the hypertrophic adipose tissue and fatty liver.\(^{32-35}\) It was recently determined that obesity correlates with chronic, low-grade inflammation, suggesting that inflammation is necessary for obesity-associated insulin resistance and the subsequent onset of type 2 DM. During the development of obesity, macrophages permeate white adipose tissue and, together with adipocytes, secrete various proinflammatory cytokines and chemokines. For instance, the visceral adipose tissue secretes resistin, interleukin (IL)-6, tumor necrosis factor (TNF-\(\alpha\)), IL-1\(\beta\), and monocyte chemoattractant protein (MCP)-1, of which TNF-\(\alpha\) and IL-6 have been demonstrated to impair insulin sensitivity. Moreover, MCP-1—an adipocyte-secreted chemokine—induces insulin resistance.\(^{53,54,56-58}\) Importantly, the visceral adipose tissue in obese individuals is infiltrated by macrophages that cooperate in generating and sustaining the inflammatory response.\(^{59-61}\) Several studies have identified different polarization states of infiltrating macrophages within the adipose tissue. In general, most macrophages classically activated by proinflammatory lipopolysaccharide (LPS) or interferon (IFN)-\(\gamma\) are known as M1 macrophages, while those alternatively activated macrophages developed in response to IL-4 or IL-13 are known as M2 macrophages. The latter can elicit anti-inflammatory activity through the secretion of IL-10.\(^{62}\) Within the obese adipose tissue, macrophages can also be activated by saturated fatty acids in the obese adipose tissue through toll-like receptor (TLR) 4 to promote a phenotypic change from M2 to M1, which subsequently enhances the proinflammatory response.\(^{63-66}\) Furthermore, monocytes in obese patients with or without type 2 DM exhibit more M1 markers and less M2 markers, when compared to normal controls. Accordingly, studies in diet-induced obesity animal models revealed that M2 macrophages in the adipose tissue can normalize the insulin sensitivity; thus, enhancing the development of M2 has the potential to mitigate insulin resistance.\(^{53,67,68}\)

Macrophage galectin-3 is an important regulator of polarization. M2 polarization by IL-4 is inhibited by galectin-3 ablation in bone marrow-derived macrophages isolated from 129sv mice. Consistently, IL-4-treated macrophages exhibited increased galectin-3 expression and secretion.\(^{69}\) Similar findings have also been made using human monocyte-differentiated macrophages. For this, human macrophages were treated with granulocyte macrophage colony-stimulating factor (GM-CSF), IFN-\(\gamma\)/LPS or macrophage colony-stimulating factor (M-CSF), and IL-4 or IL-10 to polarize into M1, M2a, and M2c, respectively. Notably, all three macrophage subtypes displayed an increase in galectin-3 in the cytosol, with a 10-fold higher expression level in M2a and M2c macrophages, compared to M1 macrophages. Nevertheless, galectin-3 secretion by M2a and M2c macrophages was ~50% and ~30% lower than M1 macrophages, respectively.\(^{70}\) Galectin-3 plays important roles in promoting both M2 and M1 macrophage polarization, and expression levels of galectin-3 are increased when cells are polarized to these two populations. These results demonstrate that galectin-3 may have both proinflammatory (promote M1 polarization) and anti-inflammatory roles (enhance M2 polarization) in macrophages.

**Diabetes mellitus.** In clinical studies, circulating galectin-3 was higher in type 2 DM patients\(^{71-74}\) and thought to be a risk factor for vascular complications, such as heart failure, nephropathy, peripheral artery disease, and other vascular complications.\(^{71}\) Patients with galectin-3 level >25 ng/mL exhibited a 11.4-fold higher risk of microvascular complications (retinopathy and/or nephropathy) and a 8.5-fold increased risk of macrovascular complications (myocardial infarction, angina pectoris, cerebrovascular event, and peripheral artery disease) compared to patients with galectin-3 level <10 ng/mL.\(^{71}\) The order of circulating level of glectin-3 was as follows: diabetes > prediabetes > normal control. Therefore, it has since been considered as a marker for prediabetes.\(^{72}\) In diabetic patients, galectin-3 concentrations were significantly elevated in subjects with coronary artery disease and associated with the formation of diseased vessels and plaques.\(^{74}\) Darrow et al found that mice developed hyperglycemia since week 2 of high-fat diet feeding, which was indicated by a threefold increase in homeostasis model assessment for insulin resistance (HOMA-IR) index and a 1.5-fold decrease in Akt activation. The authors also found increased galectin-3 expression in endothelial cells as well as circulating galectin-3 in high-fat diet-fed mice, suggesting that galectin-3 plays a role in the vascular response in DM (Table 1).\(^{73}\)

**Galectin-3 increases severity of DM.** Another report found increased galectin-3 expression in mice fed with a high-fat diet and recombinant human galectin-3 promoted preadipocyte proliferation.\(^{76}\) Intracellular galectin-3 was found to directly interact with peroxisome proliferator-activator receptor (PPAR)-\(\gamma\), an important regulator of adipocyte differentiation. The transactivation activities of galectin-3 and PPAR-\(\gamma\) complex were confirmed in HEK293 cells transfected with a PPAR-\(\gamma\) response element reporter assay. When galectin-3 was downregulated by shRNA, the transactivation activity was significantly reduced compared with cells transfected with control plasmid. Accordingly, galectin-3 ablation significantly reduced the PPAR-\(\gamma\) translocation into the nucleus, as well as its transactivation activity. Moreover, galectin-3 knockout mice exhibited less weight gain when fed with a high-fat diet. The expression levels of PPAR-\(\gamma\), CCAAT-enhancer-binding protein alpha (C/EBP\(\alpha\)), CCAAT-enhancer-binding protein beta (C/EBP\(\beta\)), and fatty acid binding protein 4 (Fabp4) were also reduced in the adipose tissue of galectin-3 knockout mice fed with a high-fat diet.\(^{77}\) Galectin-3 upregulation was also found in hepatocytes treated with 100 mM d-glucose and in the sera of patients with type 2 DM.\(^{78}\) Consistently,
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Table 1. Roles of galectin-3 in diabetes and obesity.

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galactin-3 ablation protected mice from the development of streptozotocin-induced type 1 DM. 79

Galectin-3 decreases severity of DM. Conversely, galectin-3 plays a protective role in some metabolic diseases, such as type 2 DM. In a study of 20 patients, Ohkura et al measured the glucose disposal rate, fasting insulin, HOMA-IR, insulin sensitivity index, galectin-3, and adiponectin. Notably, galectin-3 levels negatively correlated with fasting insulin ($R = -0.56, P < 0.01$) and HOMA-IR ($R = -0.52, P < 0.05$), but positively correlated with glucose disposal rate ($R = 0.71, P < 0.001$), insulin sensitivity index ($R = 0.62, P < 0.005$), and serum adiponectin level ($R = 0.61, P < 0.05$). 80 Moreover, body weight, amount of total visceral adipose tissue, fasting blood glucose, and insulin levels increased in high-fat diet-fed galectin-3 knockout mice. These mice also displayed enhanced Th1 T-cells and natural killer T (NKT) cells, as well as proinflammatory CD11c+CD11b+ macrophages, whereas the number of anti-inflammatory CD4+CD25+FoxP3+...
regulatory T-cells and M2 macrophages were reduced. Infiltrating pancreatic and peritoneal macrophages also exhibited significant increases in NLR family, pyrin domain containing 3 (NLRP3) inflammasome, nuclear factor-κB activity, and IL-1β production. Galectin-3 deficiency in mice led to the accumulation of fat as well as increased inflammation in adipose tissue, which is important in promoting insulin resistance. There were higher numbers of infiltrated macrophages and inflammatory cytokines, IL-6 and TNF-α, in the adipose tissue. High-fat diet also attenuated the expression of adiponectin and PPAR-γ in the adipose tissue. Furthermore, galectin-3 deficiency was also found to suppress endothelial glucose transporter, type 4 (GLUT4) expression and promote insulin resistance in high-fat diet-fed mice, as suggested by comparing galectin-3 knockout mice to wild-type controls.

Coronary artery disease.
Galectin-3 increases severity of coronary artery disease. Circulating galectin-3 is elevated in patients with unstable coronary artery disease as compared to stable counterparts and associated with the number of compromised vessels, indicating that galectin-3 may be a marker for the destabilization of atherosclerotic plaques. Smooth muscle cell proliferation and migration in the arterial intima is the hallmark of atherosclerosis. Galectin-3 was not expressed in quiescent smooth muscle cells but was found in the aortas of hypercholesterolemic rabbits and in the aortas of rats after balloon injury. The increase in the expression of galectin-3 in smooth muscle cells could promote monocyte chemotaxis into the arterial intima by increasing the expression levels of chemokine (C-C motif) ligand (CCL) 2, CCL8, CCL5, CCL20, and IL8. Galectin-3 was also found to be expressed in macrophages in the aortic tissue of apolipoprotein E (ApoE) knockout mice fed with a high-fat diet. In asymptomatic patients, circulating galectin-3 expression levels were associated with NADPH oxidase-dependent superoxide production (P < 0.001) and were also correlated with carotid intima-media thickness, a marker of atherosclerosis (P < 0.001). In patients with carotid atherosclerosis, galectin-3 level was also higher when compared to that of control subjects. Moreover, galectin-3 was associated with higher risk for cardiovascular mortality (hazard ratio = 2.24, 95% confidence interval: 1.06–4.73, P < 0.05). When Ozturk et al evaluated the relationship between plasma galectin-3 levels and coronary artery disease, coronary plaque burden, and plaque structures in type 2 DM patients, they found higher galectin-3 levels in patients with coronary artery disease (P < 0.001) in type 2 DM patients, which correlated with the total number of diseased vessels and plaques (P < 0.001). These data suggest that galectin-3 may also be a predictive marker for coronary plaques in patients with atherosclerosis.

Consistently, increased galectin-3 expression was found in the balloon-injured aortas of atherosclerotic rats. Galectin-3 and ApoE double-knockout mice aged 36–44 weeks showed significantly reduced amount of atherosclerotic lesions (P < 0.004) and fewer aortic atheromatous plaques (P < 0.008) when compared with ApoE knockout mice. The perivascular inflammatory infiltrates were also lowered in galectin-3 and ApoE double-knockout mice. MacKinnon et al fed galectin-3 and ApoE double-knockout mice with a high-fat diet. They found a 57% reduction in atherosclerotic lesion formation in the thoracic aorta and 50% reduction in brachiocephalic arteries. The transition from M1 (six weeks) to M2 (20 weeks) polarization was inhibited by galectin-3 ablation in ApoE knockout mice, while treating ApoE knockout mice with citrus pectin reduced plaque volume. However, as mentioned earlier, the latter does not definitely establish the role of galectin-3 due to the uncertain specificity of citrus pectin.

Galectin-3 increases severity of coronary artery disease. Lower galectin-3 expression level was found to be a risk factor in developing atherosclerosis. Kadoglou et al found a lower intraplaque expression of galectin-3 in patients with symptomatic atherosclerosis compared with those without symptoms (4.89% ± 1.60% vs. 12.01% ± 5.91%, P < 0.001). Moreover, more atherosclerotic lesions were found in galectin-3 knockout mice fed with an atherogenic high-fat diet for eight months, along with greater macrophage infiltrations and an increased accumulation of oxidized LDLs and lipoxidation products (Table 2).

Galectin-3 in the Pathogenesis of Allergic Diseases
Asthma and allergic diseases, such as allergic rhinitis and atopic dermatitis, are chronic inflammatory diseases with complex etiology that activate multiple immunological and inflammatory pathways. Both asthma and allergic diseases involve Th2-lymphocyte polarized and IL-5-mediated eosinophilic responses. Notably, galectin-3 has been shown to modulate allergic inflammatory responses.

Galectin-3 expression is associated with increased severity of allergic disease. Immediate hypersensitivity reactions are primarily mediated by mast cells and the genetic ablation of galectin-3 has been shown to decrease histamine and IL-4 secretions by IgE-activated mast cells. Moreover, the attenuated IL-4 expression was the result of diminished JNK1 expression, indicating that galectin-3 might regulate JNK1 transcription. Furthermore, galectin-3 knockout mice also developed less pronounced passive cutaneous anaphylaxis. In addition, epidermal thickness and eosinophils and mononuclear cells infiltration were significantly lower in the skin of galectin-3 knockout mice in a model of ovalbumin (OVA)-induced atopic dermatitis. Knockout mice displayed abrogated Th2, but enhanced Th1 responses as indicated by low IL-4 and high IFN-γ and IL-12 expression.

Similar results were found in an OVA-induced asthma model, where infiltration of eosinophils, macrophages, and neutrophils was significantly lower in BAL of galectin-3 knockout mice. Additionally, the concentrations of IgE, IL-4, and IFN-γ in BAL were lower in galectin-3 knockout mice, indicative of attenuated Th2 responses. Galectin-3 was also...
patients have atherosclerosis have significantly higher serum galectin-3 levels than healthy subjects.

Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and coronary atherosclerosis in Italy

Increased severity

Patients with unstable coronary artery disease have higher levels of serum galectin-3; the levels are correlated with the number of vessels compromised.

Rabbit and rat/hypercholesterolemic rabbits and rat aortas after balloon injury were used

Increased severity

Hypercholesterolemic rabbits have increased galectin-3 levels in aorta smooth muscle cells; rats after balloon injury have higher levels of galectin-3 in the aorta.

Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and atherosclerosis in Spain

Increased severity

Patients with atherosclerosis have higher levels of galectin-3 in plasma than healthy subjects.

Mouse/ApoE deficiency and ApoE and galectin-3 double-knockout mice were fed with a high-fat diet

Increased severity

Galectin-3/ApoE double-knockout mice develop less severe atherosclerosis compared with ApoE knockout mice.

Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and atherosclerosis in Greece

Decreased severity

Patients with unstable carotid plaques have lower galectin-3 levels; long-term statin treatment increases galectin-3 expression associated with stabilization of the plaques.

Mouse/galectin-3 wild type and knockout mice fed with a high-fat diet

Decreased severity

Galectin-3 knockout mice develop more severe atherosclerosis compared with wild-type mice.

shown to participate in eosinophil trafficking, an important part of allergic inflammation, through interaction with VCAM1 and α4 integrin.93

Galectin-3 gene transfer leads to decreased severity of allergic diseases. In contrast, a group of researchers in Spain published a series of papers on using galectin-3 gene therapy to treat an asthma model by OVA sensitization in brown Norway rats.96–98 Both acute and chronic airway (intranasal OVA administration for 12 weeks) inflammation were reduced in galectin-3 overexpressed rats. The effects were through reduced eosinophil infiltration into the lung, lowered IL-5, and suppressors of cytokine signaling (SOCS)-1 and SOCS-3 expression levels in the lungs.96–98 However, the discrepancy between these results and those from studies of endogenous galectin-3 could be due to the difference in the pattern of galectin-3 expression in various cell types.

There are controversial results with regard to the roles of galectin-3 in the pathogenesis of DM, atherosclerosis, and allergic diseases. In clinical studies, differences in patient ethnicity, gender, age, and enroll criteria may result in varying results. A confirmation study with a larger number of patients should be conducted to confirm these roles of galectin-3. Alternatively, the differences are conspicuous in laboratory animal models. Differences in genetic background, diet, age, sex, duration of high-fat diet, and experimental end point could have dramatic effects on the results; thus, repeating these experiments in different laboratories would likely improve the validity of the results.

Conclusion

Galectin-3 manipulation has significant effects on the regulation of inflammatory responses. Through its proinflammatory roles, it contributes to the pathogenesis of various diseases, including metabolic and allergic diseases, as well as fibrosis. Thus, galectin-3 could be a potential target for the treatment of various acute and chronic inflammatory diseases.

Author Contributions

Wrote the first draft of the manuscript: LW. Contributed to the writing of the manuscript: LW and FTL. Agree with the manuscript results and conclusions: LW and FTL. Jointly developed the structure and arguments for the paper: LW and FTL. Made critical revisions and approved final version: FTL. All authors reviewed and approved of the final manuscript.

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