Galectin-3 and Inflammation

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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

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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,[1–3] 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, glycan 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.[13] Conversely, activation of human monocytes by lipopolysaccharide and interferon-γ suppressed galectin-3 expression.[14] THP-1 cells treated with nonsteroidal or corticosteroidal anti-inflammatory drugs showed a lowered expression level of galectin-3.[15–17] The expression levels of galectin-3 are low or undetectable in resting B- and T-cells,[18,19] but upregulated when these cells are activated.[19]

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.[20] (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.[21] (5) Extracellular galectin-3 enhances the adhesion between neutrophils and laminin and activate monocytes.[22,23] (6) Exogenous galectin-3 enhances endothelial cell capillary tube formation to promote angiogenesis.[24]

Many studies have shown that galectin-3 may regulate inflammation through a variety of mechanisms.[25–31] 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 endothelium 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.[32] 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 (K_d = 14 nM).[33]

Hermansky–Pudlak syndrome (HPS) is an autosomal recessive disorder characterized by oculocutaneous 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.[34]

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.[35]

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.[36] 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.[37] 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.[38] 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).[39] 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.[40] 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,

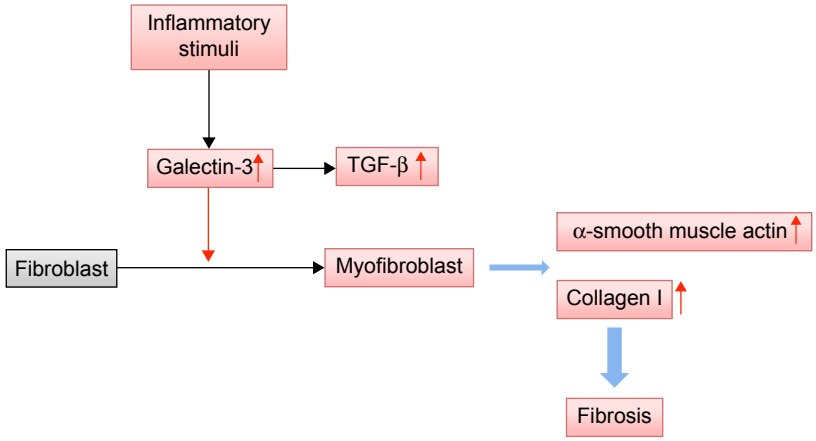

Figure 1. Roles of galectin-3 in fibrogenesis. Inflammatory stimuli in the lung, heart, and liver increase the expression level of galectin-3, which in turn promote fibroblasts to differentiate into myofibroblasts. Myofibroblasts express α-smooth muscle actin and are important sources of collagen I in active fibrotic region. Galectin-3 overexpression also stimulates the expression of TGF-β, which could activate myofibroblast to promote fibrosis.

hypertension, glucose intolerance and toxicity, hepatic steatosis, atherogenic dyslipidemia, and type 2 diabetes mellitus (DM).[52–55] 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.[52–55] 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)-α, IL-1β, and monocyte chemoattractant protein (MCP)-1, of which TNF-α 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 responses.[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)-γ 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-γ/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 infraction, 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).[75]

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-activated receptor (PPAR)-γ, an important regulator of adipocyte differentiation. The transactivation activities of galectin-3 and PPAR-γ complex were confirmed in HEK293 cells transfected with a PPAR-γ 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-γ translocation into the nucleus, as well as its transactivation activity. Moreover, galecitin-3 knockout mice exhibited less weight gain when fed with a high-fat diet. The expression levels of PPAR-γ, CCAAT-enhancer-binding protein alpha (C/EBPα), CCAAT-enhancer-binding protein beta (C/EBPβ), 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,

Table 1. Roles of galectin-3 in diabetes and obesity.

SPECIES/STRATEGIES USED	CONTRIBUTION OF GALECTIN-3 TO DISEASE OUTCOME	MAIN MEASURE OUTCOME	REFERENCE(S)
Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and vascular disease in type 2 DM patients in China	Increased severity	Diabetes patients have higher serum galectin-3 levels than control subjects. Diabetes patients with high serum galectin-3 levels have a higher risk of developing heart failure, nephropathy, and peripheral arterial disease.	71
Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and pre-diabetes and/or diabetes patients in Turkey	Increased severity	Pre-diabetes and diabetes patients have higher serum galectin-3 levels than healthy subjects.	72
Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and structural myocardial alterations in diabetes patients in Serbia	Increased severity	Patients with type 2 DM and arterial hypertension have significantly elevated levels of serum galectin-3.	73
Mouse/high-fat diet-induced type 2 diabetes	Increased severity	High-fat diet causes higher levels of galectin-3 in the endothelium and serum.	75
Mouse/adipose tissue in high-fat diet fed mice; human/adipocytes	Increased severity	High fat diet induces galectin-3 expression in adipose tissues in mice. Human recombinant galectin-3 promotes proliferation of human primary preadipocytes.	76
Mouse/galectin-3 wild type and knockout mice fed with high-fat diet	Increased severity	Galectin-3 knockout mice have lower body weight and epididymal white adipose tissue after being fed a high-fat diet, compared to wild-type mice.	77
Liver cell/high-glucose induced proteome alteration	Increased severity	High glucose (25 and 100 mM) induces galectin-3 in liver cells.	78
Mouse/streptozotocin-induced diabetes in galectin-3 knockout mice	Increased severity	Galectin-3 knockout mice exhibit resistant to streptozotocin-induced diabetogenesis	79
Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and type 2 diabetes patients in Japan	Decreased severity	Patients with type 2 diabetes have significantly lower levels of serum galectin-3	80
Mouse/galectin-3 wild type and knockout mice fed with high-fat diet	Decreased severity	Galectin-3 knockout mice have increased body weight, visceral adipose tissue, and inflammation in adipose tissue after being fed a high-fat diet, compared to wild-type mice.	81
Mouse/galectin-3 wild type and knockout mice fed with high-fat diet	Decreased severity	Galectin-3 knockout mice exhibit increased adiposity, systemic inflammation and impaired fasting glucose after high-fat diet.	82
Mouse/galectin-3 wild type and knockout mice fed with high-fat diet	Decreased severity	Galectin-3 knockout mice show hyperglycemia and impaired glucose tolerance after high-fat diet, compared to wild-type mice.	83

galectin-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.[81] 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.[82] Furthermore, galecitin-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.[83]

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.[84] 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.[85] 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.[86] 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, $P < 0.05$).[87] 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 galactin-3 may also be a predictive marker for coronary plaques in patients with atherosclerosis.[74]

Consistently, increased galectin-3 expression was found in the balloon-injured aortas of atherosclerotic rats.[85] 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.[88] 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.[89] 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 decreases 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%, $P < 0.001$).[90] 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).[91]

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 diseases. 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.[92] 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.[93]

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.[94] Galectin-3 was also

Table 2. Roles of galectin-3 in coronary artery disease.

SPECIES/STRATEGIES USED	CONTRIBUTION OF GALECTIN-3 TO DISEASE OUTCOME	MAIN MEASURE OUTCOME	REFERENCE(S)
Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and coronary atherosclerosis patients in Turkey	Increased severity	Patients with coronary artery disease have significantly higher serum galectin-3 levels than healthy subjects.	74
Human/A population-based cross-sectional survey to investigate the relationship between serum galectin-3 and coronary artery disease 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.	84
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.	85
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.	87
Mouse/Apolipoprotein E (ApoE)-deficient 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.	89
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.	90
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.	91

shown to participate in eosinophil trafficking, an important part of allergic inflammation, through interaction with VCAM1 and α4 integrin.[95]

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 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.

REFERENCES

1. Liu FT, Rabinovich GA. Galectins: regulators of acute and chronic inflammation. *Ann N Y Acad Sci*. 2010;1183:158–182.
2. Yang RY, Liu FT. Galectins in cell growth and apoptosis. *Cell Mol Life Sci*. 2003; 60(2):267–276.
3. Compagno D, Jaworski FM, Gentilini L, et al. Galectins: major signaling modulators inside and outside the cell. *Curr Mol Med*. 2014;14(5):630–651.

4. Hoja-Lukowicz D, Kedracka-Krok S, Duda W, Litynska A. The lectin-binding pattern of nucleolin and its interaction with endogenous galectin-3. *Cell Mol Biol Lett*. 2014;19(3):461–482.
5. Mishra BB, Li Q, Steichen AL, et al. Galectin-3 functions as an alarmin: pathogenic role for sepsis development in murine respiratory tularemia. *PLoS One*. 2013;8(3):e59616.
6. Hsu DK, Chernyavsky AI, Chen HY, Yu L, Grando SA, Liu FT. Endogenous galectin-3 is localized in membrane lipid rafts and regulates migration of dendritic cells. *J Invest Dermatol*. 2009;129(3):573–583.
7. Woo HJ, Lotz MM, Jung JU, Mercurio AM. Carbohydrate-binding protein 35 (Mac-2), a laminin-binding lectin, forms functional dimers using cysteine 186. *J Biol Chem*. 1991;266(28):18419–18422.
8. Ahmad N, Gabius HJ, André S, et al. Galectin-3 precipitates as a pentamer with synthetic multivalent carbohydrates and forms heterogeneous cross-linked complexes. *J Biol Chem*. 2004;279(12):10841–10847.
9. Nieminen J, Kuno A, Hirabayashi J, Sato S. Visualization of galectin-3 oligomerization on the surface of neutrophils and endothelial cells using fluorescence resonance energy transfer. *J Biol Chem*. 2007;282(2):1374–1383.
10. Dumic J, Dabelic S, Flogel M. Galectin-3: an open-ended story. *Biochim Biophys Acta*. 2006;1760(4):616–635.
11. Abedin MJ, Kashio Y, Seki M, Nakamura K, Hirashima M. Potential roles of galectins in myeloid differentiation into three different lineages. *J Leukoc Biol*. 2003;73(5):650–656.
12. Elliott MJ, Strasser A, Metcalf D. Selective up-regulation of macrophage function in granulocyte-macrophage colony-stimulating factor transgenic mice. *J Immunol*. 1991;147(9):2957–2963.
13. Reichert F, Rotshenker S. Galectin-3/MAC-2 in experimental allergic encephalomyelitis. *Exp Neurol*. 1999;160(2):508–514.
14. Liu FT, Hsu DK, Zuberi RI, Kuwabara I, Chi EY, Henderson WR Jr. Expression and function of galectin-3, a beta-galactoside-binding lectin, in human monocytes and macrophages. *Am J Pathol*. 1995;147(4):1016–1028.
15. Dabelic S, Supraha S, Dumic J. Galectin-3 in macrophage-like cells exposed to immunomodulatory drugs. *Biochim Biophys Acta*. 2006;1760(4):701–709.
16. Dabelic S, Novak R, Goreta SS, Dumic J. Galectin-3 expression in response to LPS, immunomodulatory drugs and exogenously added galectin-3 in monocyte-like THP-1 cells. *In Vitro Cell Dev Biol Anim*. 2012;48(8):518–527.
17. Maldonado CA, Sundblad V, Salatino M, et al. Cell-type specific regulation of galectin-3 expression by glucocorticoids in lung Clara cells and macrophages. *Histol Histopathol*. 2011;26(6):747–759.
18. Liu FT, Albrandt K, Mendel E, Kulczycki A Jr, Orida NK. Identification of an IgE-binding protein by molecular cloning. *Proc Natl Acad Sci U S A*. 1985; 82(12):4100–4104.
19. Joo HG, Goedegebuure PS, Sadanaga N, Nagoshi M, von Bernstorff W, Eberlein TJ. Expression and function of galectin-3, a beta-galactoside-binding protein in activated T lymphocytes. *J Leukoc Biol*. 2001;69(4):555–564.
20. Yang RY, Hsu DK, Liu FT. Expression of galectin-3 modulates T-cell growth and apoptosis. *Proc Natl Acad Sci U S A*. 1996;93(13):6737–6742.
21. Akahani S, Nangia-Makker P, Inohara H, Kim HR, Raz A. Galectin-3: a novel antiapoptotic molecule with a functional BH1 (NWGR) domain of Bcl-2 family. *Cancer Res*. 1997;57(23):5272–5276.
22. Nieminen J, St-Pierre C, Sato S. Galectin-3 interacts with naive and primed neutrophils, inducing innate immune responses. *J Leukoc Biol*. 2005;78(5): 1127–1135.
23. Danella Polli C, Alves Toledo K, Franco LH, et al. Monocyte migration driven by galectin-3 occurs through distinct mechanisms involving selective interactions with the extracellular matrix. *ISRN Inflamm*. 2013;2013:259256.
24. Nangia-Makker P, Honjo Y, Sarvis R, et al. Galectin-3 induces endothelial cell morphogenesis and angiogenesis. *Am J Pathol*. 2000;156(3):899–909.
25. Young CC, Al-Dalahmah O, Lewis NJ, et al. Blocked angiogenesis in galectin-3 null mice does not alter cellular and behavioral recovery after middle cerebral artery occlusion stroke. *Neurobiol Dis*. 2014;63:155–164.
26. Sanchez-Ruderisch H, Fischer C, Detjen KM, et al. Tumor suppressor p16 INK4a: downregulation of galectin-3, an endogenous competitor of the pro-anoikis effector galectin-1, in a pancreatic carcinoma model. *FEBS J*. 2010; 277(17):3552–3563.
27. Koch A, Poirier F, Jacob R, Delacour D. Galectin-3, a novel centrosome-associated protein, required for epithelial morphogenesis. *Mol Biol Cell*. 2010;21(2): 219–231.
28. Liu L, Sakai T, Tran NH, Mukai-Sakai R, Kaji R, Fukui K. Nucling interacts with nuclear factor-kappaB, regulating its cellular distribution. *FEBS J*. 2009;276(5):1459–1470.
29. Saegusa J, Hsu DK, Liu W, et al. Galectin-3 protects keratinocytes from UVB-induced apoptosis by enhancing AKT activation and suppressing ERK activation. *J Invest Dermatol*. 2008;128(10):2403–2411.
30. Funasaka T, Balan V, Raz A, Wong RW. Nucleoporin Nup98 mediates galectin-3 nuclear-cytoplasmic trafficking. *Biochem Biophys Res Commun*. 2013;434(1): 155–161.
31. Wang Y, Balan V, Kho D, Hogan V, Nangia-Makker P, Raz A. Galectin-3 regulates p21 stability in human prostate cancer cells. *Oncogene*. 2013;32(42): 5058–5065.
32. Kasper M, Hughes RC. Immunocytochemical evidence for a modulation of galectin 3 (Mac-2), a carbohydrate binding protein, in pulmonary fibrosis. *J Pathol*. 1996;179(3):309–316.
33. Mackinnon AC, Gibbons MA, Farnworth SL, et al. Regulation of transforming growth factor-beta1-driven lung fibrosis by galectin-3. *Am J Respir Crit Care Med*. 2012;185(5):537–546.
34. Cullinane AR, Yeager C, Dorward H, et al. Dysregulation of galectin-3. Implications for Hermansky-Pudlak syndrome pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2014;50(3):605–613.
35. Ge XN, Bahaie NS, Kang BN, et al. Allergen-induced airway remodeling is impaired in galectin-3-deficient mice. *J Immunol*. 2010;185(2):1205–1214.
36. Li LC, Li J, Gao J. Functions of galectin-3 and its role in fibrotic diseases. *J Pharmacol Exp Ther*. 2014;351(2):336–343.
37. Henderson NC, Mackinnon AC, Farnworth SL, et al. Galectin-3 regulates myofibroblast activation and hepatic fibrosis. *Proc Natl Acad Sci U S A*. 2006; 103(13):5060–5065.
38. de Oliveira SA, de Freitas Souza BS, Sá Barreto EP, et al. Reduction of galectin-3 expression and liver fibrosis after cell therapy in a mouse model of cirrhosis. *Cytotherapy*. 2012;14(3):339–349.
39. Traber PG, Chou H, Zomer E, et al. Regression of fibrosis and reversal of cirrhosis in rats by galectin inhibitors in thioacetamide-induced liver disease. *PLoS One*. 2013;8(10):e75361.
40. Traber PG, Zomer E. Therapy of experimental NASH and fibrosis with galectin inhibitors. *PLoS One*. 2013;8(12):e83481.
41. Iacobini C, Menini S, Ricci C, et al. Galectin-3 ablation protects mice from diet-induced NASH: a major scavenging role for galectin-3 in liver. *J Hepatol*. 2011;54(5):975–983.
42. de Boer RA, van Veldhuisen DJ, Gansevoort RT, et al. The fibrosis marker galectin-3 and outcome in the general population. *J Intern Med*. 2012;272(1):55–64.
43. Lopez-Andrès N, Rossignol P, Iraqi W, et al. Association of galectin-3 and fibrosis markers with long-term cardiovascular outcomes in patients with heart failure, left ventricular dysfunction, and dyssynchrony: insights from the CARE-HF (cardiac resynchronization in heart failure) trial. *Eur J Heart Fail*. 2012;14(1):74–81.
44. Ho JE, Liu C, Lyass A, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. *J Am Coll Cardiol*. 2012;60(14):1249–1256.
45. Lok DJ, Van Der Meer P, de la Porte PW, et al. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. *Clin Res Cardiol*. 2010;99(5):323-328.
46. Rahmouni K, Morgan DA, Morgan GM, Mark AL, Haynes WG. Role of selective leptin resistance in diet-induced obesity hypertension. *Diabetes*. 2005; 54(7):2012–2018.
47. Correia ML, Haynes WG, Rahmouni K, Morgan DA, Sivitz WI, Mark AL. The concept of selective leptin resistance: evidence from agouti yellow obese mice. *Diabetes*. 2002;51(2):439–442.
48. Martínez-Martínez E, Jurado-López R, Valero-Muñoz M, et al. Leptin induces cardiac fibrosis through galectin-3, mTOR and oxidative stress: potential role in obesity. *J Hypertens*. 2014;32(5):1104–1114.
49. Calvier L, Miana M, Reboul P, et al. Galectin-3 mediates aldosterone-induced vascular fibrosis. *Arterioscler Thromb Vasc Biol*. 2013;33(1):67–75.
50. Ferrer MF, Pascuale CA, Gomez RM, Leguizamon MS. DTU I isolates of *Trypanosoma cruzi* induce upregulation of galectin-3 in murine myocarditis and fibrosis. *Parasitology*. 2014;141(6):849–858.
51. Pineda MA, Cuervo H, Fresno M, Soto M, Bonay P. Lack of galectin-3 prevents cardiac fibrosis and effective immune responses in a murine model of *Trypanosoma cruzi* infection. *J Infect Dis*. 2015;212(7):1160–1171.
52. Boden G, She P, Mozzoli M, et al. Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor-kappaB pathway in rat liver. *Diabetes*. 2005;54(12):3458–3465.
53. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest*. 2006;116(7):1793–1801.
54. Shoelson SE, Lee J, Yuan M. Inflammation and the IKK beta/I kappa B/NF-kappa B axis in obesity- and diet-induced insulin resistance. *Int J Obes Relat Metab Disord*. 2003;27(suppl 3):S49–S52.
55. Zemel MB, Donnelly JE, Smith BK, et al. Effects of dairy intake on weight maintenance. *Nutr Metab (Lond)*. 2008;5:28.
56. Herrero L, Shapiro H, Nayer A, Lee J, Shoelson SE. Inflammation and adipose tissue macrophages in lipodystrophic mice. *Proc Natl Acad Sci U S A*. 2010; 107(1):240–245.
57. Sun X, Zemel MB. Calcitriol and calcium regulate cytokine production and adipocyte-macrophage cross-talk. *J Nutr Biochem*. 2008;19(6):392-399.
58. Zemel MB, Sun X, Sobhani T, Wilson B. Effects of dairy compared with soy on oxidative and inflammatory stress in overweight and obese subjects. *Am J Clin Nutr*. 2010;91(1):16–22.

59. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003;112(12):1796–1808.
60. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;112(12):1821–1830.
61. Clément K, Viguerie N, Poitou C, et al. Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *FASEB J*. 2004;18(14): 1657–1669.
62. Huang JY, Chiang MT, Yet SF, Chau LY. Myeloid heme oxygenase-1 haploinsufficiency reduces high fat diet-induced insulin resistance by affecting adipose macrophage infiltration in mice. *PLoS One*. 2012;7(6):e38626.
63. Lumeng CN, DelProposto JB, Westcott DJ, Saltiel AR. Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. *Diabetes*. 2008;57(12):3239–3246.
64. Odegaard JI, Ricardo-Gonzalez RR, Red Eagle A, et al. Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. *Cell Metab*. 2008;7(6):496–507.
65. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, et al. Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. *Nature*. 2007;447(7148):1116–1120.
66. Kang K, Reilly SM, Karabacak V, et al. Adipocyte-derived Th2 cytokines and myeloid PPARdelta regulate macrophage polarization and insulin sensitivity. *Cell Metab*. 2008;7(6):485–495.
67. Nishimura S, Manabe I, Nagasaki M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med*. 2009;15(8):914–920.
68. Roth CL, Kratz M, Ralston MM, Reinehr T. Changes in adipose-derived inflammatory cytokines and chemokines after successful lifestyle intervention in obese children. *Metabolism*. 2010;60(4):445–452.
69. MacKinnon AC, Farnworth SL, Hodkinson PS, et al. Regulation of alternative macrophage activation by galectin-3. *J Immunol*. 2008;180(4):2650–2658.
70. Novak R, Dabelic S, Dumic J. Galectin-1 and galectin-3 expression profiles in classically and alternatively activated human macrophages. *Biochim Biophys Acta*. 2012;1820(9):1383–1390.
71. Jin QH, Lou YF, Li TL, Chen HH, Liu Q, He XJ. Serum galectin-3: a risk factor for vascular complications in type 2 diabetes mellitus. *Chin Med J (Engl)*. 2013;126(11):2109–2115.
72. Yilmaz H, Cakmak M, Inan O, Darcin T, Akcay A. Increased levels of galectin-3 were associated with prediabetes and diabetes: new risk factor? *J Endocrinol Invest*. 2014;38(5):527–533.
73. Seferovic JP, Lalic NM, Floridi F, et al. Structural myocardial alterations in diabetes and hypertension: the role of galectin-3. *Clin Chem Lab Med*. 2014;52(10): 1499–1505.
74. Ozturk D, Celik O, Satilmis S, et al. Association between serum galectin-3 levels and coronary atherosclerosis and plaque burden/structure in patients with type 2 diabetes mellitus. *Coron Artery Dis*. 2015;26(5):396–401.
75. Darrow AL, Shohet RV, Maresh JG. Transcriptional analysis of the endothelial response to diabetes reveals a role for galectin-3. *Physiol Genomics*. 2011; 43(20):1144–1152.
76. Kiwaki K, Novak CM, Hsu DK, Liu FT, Levine JA. Galectin-3 stimulates preadipocyte proliferation and is up-regulated in growing adipose tissue. *Obesity (Silver Spring)*. 2007;15(1):32–39.
77. Baek JH, Kim SJ, Kang HG, et al. Galectin-3 activates PPARgamma and supports white adipose tissue formation and high-fat diet-induced obesity. *Endocrinology*. 2015;156(1):147–156.
78. Chen JY, Chou HC, Chen YH, Chan HL. High glucose-induced proteome alterations in hepatocytes and its possible relevance to diabetic liver disease. *J Nutr Biochem*. 2013;24(11):1889–1910.
79. Mensah-Brown EP, Al Rabesi Z, Shahin A, et al. Targeted disruption of the galectin-3 gene results in decreased susceptibility to multiple low dose streptozotocin-induced diabetes in mice. *Clin Immunol*. 2009;130(1):83–88.
80. Ohkura T, Fujioka Y, Nakanishi R, et al. Low serum galectin-3 concentrations are associated with insulin resistance in patients with type 2 diabetes mellitus. *Diabetol Metab Syndr*. 2014;6(1):106.
81. Pejnovic NN, Pantic JM, Jovanovic IP, et al. Galectin-3 deficiency accelerates high-fat diet-induced obesity and amplifies inflammation in adipose tissue and pancreatic islets. *Diabetes*. 2013;62(6):1932–1944.
82. Pang J, Rhodes DH, Pini M, et al. Increased adiposity, dysregulated glucose metabolism and systemic inflammation in galectin-3 KO mice. *PLoS One*. 2013; 8(2):e57915.
83. Darrow AL, Shohet RV. Galectin-3 deficiency exacerbates hyperglycemia and the endothelial response to diabetes. *Cardiovasc Diabetol*. 2015;14(1):73.
84. Falcone C, Lucibello S, Mazzucchelli I, et al. Galectin-3 plasma levels and coronary artery disease: a new possible biomarker of acute coronary syndrome. *Int J Immunopathol Pharmacol*. 2011;24(4):905–913.
85. Arar C, Gaudin JC, Capron L, Legrand A. Galectin-3 gene (LGALS3) expression in experimental atherosclerosis and cultured smooth muscle cells. *FEBS Lett*. 1998;430(3):307–311.
86. Papaspyridonos M, McNeill E, de Bono JP, et al. Galectin-3 is an amplifier of inflammation in atherosclerotic plaque progression through macrophage activation and monocyte chemoattraction. *Arterioscler Thromb Vasc Biol*. 2008;28(3): 433–440.
87. Madrigal-Matute J, Lindholt JS, Fernandez-Garcia CE, et al. Galectin-3, a biomarker linking oxidative stress and inflammation with the clinical outcomes of patients with atherothrombosis. *J Am Heart Assoc*. 2014;3(4):e000785.
88. Nachtigal M, Ghaffar A, Mayer EP. Galectin-3 gene inactivation reduces atherosclerotic lesions and adventitial inflammation in ApoE-deficient mice. *Am J Pathol*. 2008;172(1):247–255.
89. MacKinnon AC, Liu X, Hadoke PW, Miller MR, Newby DE, Sethi T. Inhibition of galectin-3 reduces atherosclerosis in apolipoprotein E-deficient mice. *Glycobiology*. 2013;23(6):654–663.
90. Kadoglou NP, Sfyroeras GS, Spathis A, et al. Galectin-3, carotid plaque vulnerability, and potential effects of statin therapy. *Eur J Vasc Endovasc Surg*. 2014; 49(1):4–9.
91. Iacobini C, Menini S, Ricci C, et al. Accelerated lipid-induced atherogenesis in galectin-3-deficient mice: role of lipoxidation via receptor-mediated mechanisms. *Arterioscler Thromb Vasc Biol*. 2009;29(6):831–836.
92. Chen HY, Sharma BB, Yu L, et al. Role of galectin-3 in mast cell functions: galectin-3-deficient mast cells exhibit impaired mediator release and defective JNK expression. *J Immunol*. 2006;177(8):4991–4997.
93. Saegusa J, Hsu DK, Chen HY, et al. Galectin-3 is critical for the development of the allergic inflammatory response in a mouse model of atopic dermatitis. *Am J Pathol*. 2009;174(3):922–931.
94. Zuberi RI, Hsu DK, Kalayci O, et al. Critical role for galectin-3 in airway inflammation and bronchial hyperresponsiveness in a murine model of asthma. *Am J Pathol*. 2004;165(6):2045–2053.
95. Rao SP, Wang Z, Zuberi RI, et al. Galectin-3 functions as an adhesion molecule to support eosinophil rolling and adhesion under conditions of flow. *J Immunol*. 2007;179(11):7800–7807.
96. del Pozo V, Rojo M, Rubio ML, et al. Gene therapy with galectin-3 inhibits bronchial obstruction and inflammation in antigen-challenged rats through interleukin-5 gene downregulation. *Am J Respir Crit Care Med*. 2002;166(5): 732–737.
97. López E, del Pozo V, Miguel T, et al. Inhibition of chronic airway inflammation and remodeling by galectin-3 gene therapy in a murine model. *J Immunol*. 2006;176(3):1943–1950.
98. Lopez E, Zafra MP, Sastre B, Gamez C, Lahoz C, del Pozo V. Gene expression profiling in lungs of chronic asthmatic mice treated with galectin-3: down-regulation of inflammatory and regulatory genes. *Mediators Inflamm*. 2011; 2011:823279.