GALECTIN-3 IN OBESITY AND TYPE 2 DIABETES

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GALEKTIN-3 U GOJAZNOSTI I TIPU 2 DIJABETESA

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ABSTRACT

Galectin-3 is an important regulator of inflammation and acts as a receptor for advanced-glycation (AGE) and lipoxidation end-products (ALE). Evidence indicates a significant upregulation in circulating levels and visceral adipose tissue production of Galectin-3 in obesity and type 2 diabetes. Recent studies demonstrate development of obesity and dysregulation of glucose metabolism in Galectin-3 "knockout" (KO) mice, which also develop accelerated and more severe pathology in models of atherosclerosis and metabolically-induced kidney damage. Thus, evidence that Galectin-3 is an important player in metabolic disease is accumulating. This review discusses current evidence on the connection between Galectin-3 and metabolic disease, focusing on mechanisms by which this galectin modulates adiposity, glucose metabolism and obesity-associated inflammatory responses.

Keywords: *glucose metabolism, inflammation, obesity, diabetes*

SAŽETAK

Galektin-3 ima važnu ulogu u regulaciji inflamacije i predstavlja receptor za završne produkte glikacije (AGE) (engl. advanced-glycation end-products) i lipoksidacije (ALE) (engl. advanced-lipoxidation end-products). Dosadašnja istraživanja ukazuju da su cirkulišući nivoi i produkcija Galektina-3 u visceralnom masnom tkivu povišeni u gojaznosti i tipu 2 dijabetesa. Noviji eksperimentalni rezultati pokazuju ubrzan razvoj gojaznosti i poremećen metabolizam glukoze u Galektin-3 deficijentnih miševa, koji razvijaju teže oblike ateroskleroze i oštećenja bubrega u sklopu metaboličkih poremećaja, što govori u prilog značajne uloge Galektina-3 u metaboličkim bolestima. U ovom revijskom radu će biti prikazana sadašnja znanja o povezanosti Galektina-3 i metaboličkih poremećaja sa fokusom na mehanizme kojima ovaj galektin modulira visceralnu gojaznost, metabolizam glukoze i inflamaciju povezanu sa gojaznošću.

Ključne reči: *metabolizam glukoze, inflamacija, gojaznost, dijabetes*

INTRODUCTION

Metabolism and immunity preserve internal homeostasis in response to diverse environmental challenges such as excess nutrients or microbial agents by employing a similar hierarchy of processes thus exhibiting a close connection. Immune-mediated metabolic control is exerted through a complex network of immune cells located in metabolic tissues, including adipose tissue and the liver, that maintain homeostatic control under conditions of chronic overnutrition. Regulatory components that are shared between metabolism and immunity are yet incompletely understood (1). Galectins, evolutionarily conserved lectins that are produced by various cell types including immune cells and adipocytes, participate in immunometabolism (Fig. 1). This review addresses the role of Galectin-3 (Gal-3), a member of the galectin family of β-galactoside-binding proteins, in metabolic disease.

Galectin-3

A broad spectrum of roles has been attributed to galectins, including regulation of embryogenesis, angiogenesis, neurogenesis, and immunity. Their expression and secretion is altered during tumorigenesis, neurodegeneration and inflammation. The "galectin signalosome" has a role in
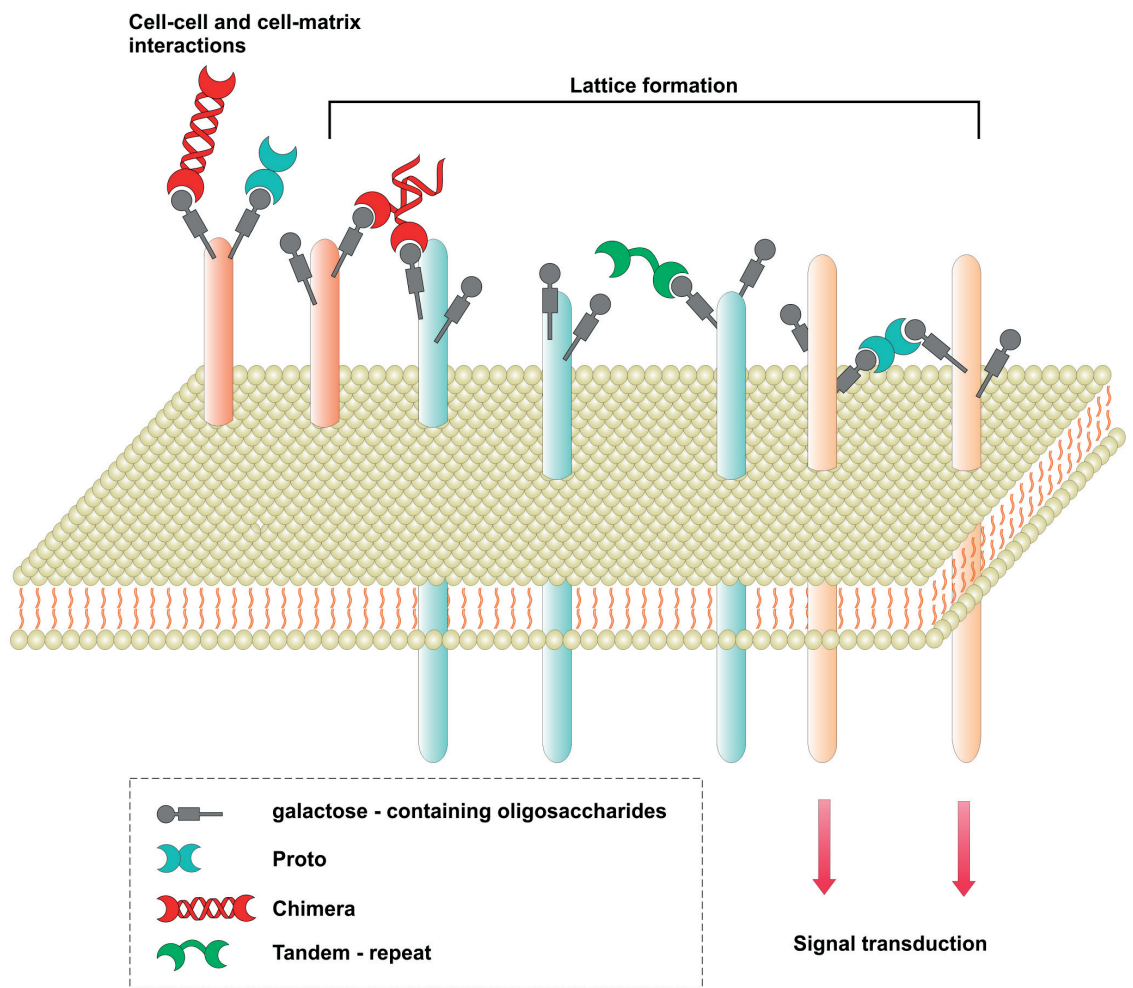
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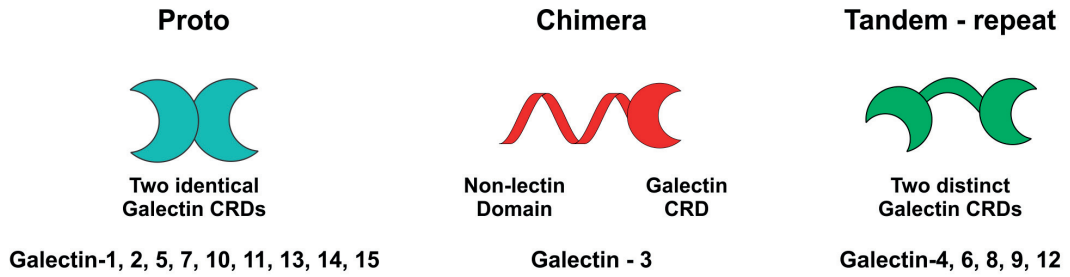
Figure 1. Galectins

Panel A: Galectins are a family of glycan binding lectins which recognize carbohydrates by conserved carbohydrate-recognition domains (CRDs). The 15 galectins which have been identified in mammals are widely distributed and have multiple roles in innate and adaptive immune responses and have been implicated in the pathogenesis of inflammatory, autoimmune and malignant disorders. Galectins are classified on the basis of their structure into three groups: prototypical galectins that contain one CRD (Galectin-1, 2, 5, 7, 10, 11, 13, 14 and 15); Galectin-3, a chimeric galectin which consists of one CRD covalently linked to tandem repeats of proline- and glycine-rich short domains; and tandem repeat galectins that contain two covalently linked CRDs connected by a small peptide domain of up to 70 aa (Galectin-4, 6, 8, 9 and 12).

Panel B: Prototypical galectins exist as dimers. Galectin-3 can both dimerize and oligomerize when it binds to multivalent carbohydrate chains, while tandem repeat galectins have two carbohydrate-binding sites. Galectins interact with transmembrane glycoconjugates and trigger intracellular signaling events; they can also bridge two cells or cells to extracellular matrix proteins and can be secreted in the extracellular space.

Table 1. Response of Gal-3 KO mice in models of metabolic disease

Model	Strains and treatments	Outcome of Gal-3 KO mice compared to WT mice	Reference
Obesity and insulin resistance	WT and Gal-3 KO mice on chow or HFD	Increased adiposity and inflammation, impaired glucose metabolism	[38,39]
Atherosclerosis	WT and Gal-3 KO mice on atherogenic diet	Increased severity	[20]
	Apo-E KO and Apo-E/Gal-3 KO on chow or high cholesterol diet	Decreased severity	[19,56]
Renal disease	WT and Gal-3 KO mice with age- , chemical- or diet-induced glomerular lesions	Increased severity	[13-15,17]
	WT and Gal-3 KO mice with ischemia-reperfusion renal injury	Decreased severity	[57]
Liver disease	WT and Gal-3 KO mice with age- or diet-related NAFLD/NASH	Increased severity	[21,22,58]
	WT and Gal-3 KO mice with age-related NAFLD/NASH	Decreased severity	[18]

many physiological and pathological conditions and better understanding of its functions could lead to development of novel therapeutic approaches that will enable control of systemic and tissue specific expression of galectins.

Galectin-3 has a unique structure in the galectin family, having both lectin-like and carbohydrate-recognition domains (CRD) (Fig. 1). Gal-3 can be present on the cell surface and intracellularly, both in the cytoplasm and the nucleus, and can also be secreted in extracellular spaces, including the systemic circulation. Gal-3 recognizes endogenous lectins, specifically cell surface β-galactosides and N-acetyllactosamine (LacNAc), and modulates intracellular signaling pathways upon cell activation, proliferation and apoptosis. In addition, Gal-3 exerts important cell-cell and cell-extracellular matrix pro-adhesive roles, while also acting as a scavenger molecule for glucose and lipid adducts and binding microbial products, including endotoxin (2).

Production of Gal-3 is altered in a variety of pathophysiological conditions in humans, including cancer, autoimmunity, endurance exercise and others (3,4). Importantly, Gal-3 is considered an excellent prognostic marker in patients with heart failure (5). Here we will focus on the regulation and role of Gal-3 in obesity and Type 2 diabetes (T2D).

Galectin-3 and inflammation

Production of Gal-3 is highly increased during inflammation in both humans and experimental animals, but the role of this galectin in modulating inflammation depends on the cell type, localization and pathophysiological condition. Thus, Gal-3 exerts pro-inflammatory effects in a variety of *in vivo* experimental models, including autoimmune disorders, acute liver injury, bacterial infections and malignancies, as demonstrated by reduced disease severity in Gal-3 KO mice (4,6-10). This evidence has led to the suggestion that Gal-3 may function as an alarmin, a

family of endogenous immunomodulatory molecules that belong to the larger family of danger-associated molecular patterns (DAMPs) (11). However, evidence that Gal-3 KO mice have exacerbated sensitivity to endotoxin (12) and heightened inflammation in response to some metabolic stimuli questions this classification (Table 1). In fact, Gal-3 KO mice develop accelerated glomerular injury induced by diabetes (13,14), advanced glycation end-products (AGE) (15,16) or ageing (17). However, in the context of atherosclerosis and hepatic steatosis, both reduced (18,19) and more pronounced (20-22) disease has been reported in Gal-3 KO mice. In situations where increased pathology is observed in Gal-3 KO mice this has been attributed to elevated oxidative stress and inflammatory responses as a result of decreased scavenging of AGE and lipoxidation end-products (ALE), increased expression of receptor for AGE (RAGE) and the consequent RAGE-dependent inflammation. Other potential protective effects of Gal-3 include its ability to enhance production of the anti-inflammatory cytokine IL-10 while suppressing the pro-inflammatory IL-17 pathway in response to microbial stimulation (23-25). Since Gal-3 directly interacts with the microflora and a variety of pathogenic bacteria (26,27), the contradictory results obtained when examining the role of Gal-3 in inflammation using Gal-3 KO mice may at least in part be the consequence of different microbial populations in colonies reared apart and/or the involvement of specific commensals in the disease pathogenesis under different experimental conditions. Given the important involvement of the microflora in a variety of pathologies, including those of metabolic origin, a better understanding of the cross-talk between Gal-3 and commensal bacteria is necessary to clarify these issues.

Galectin-3 and obesity

White adipose tissue is the main site for energy storage, where insulin controls uptake and storage of glucose
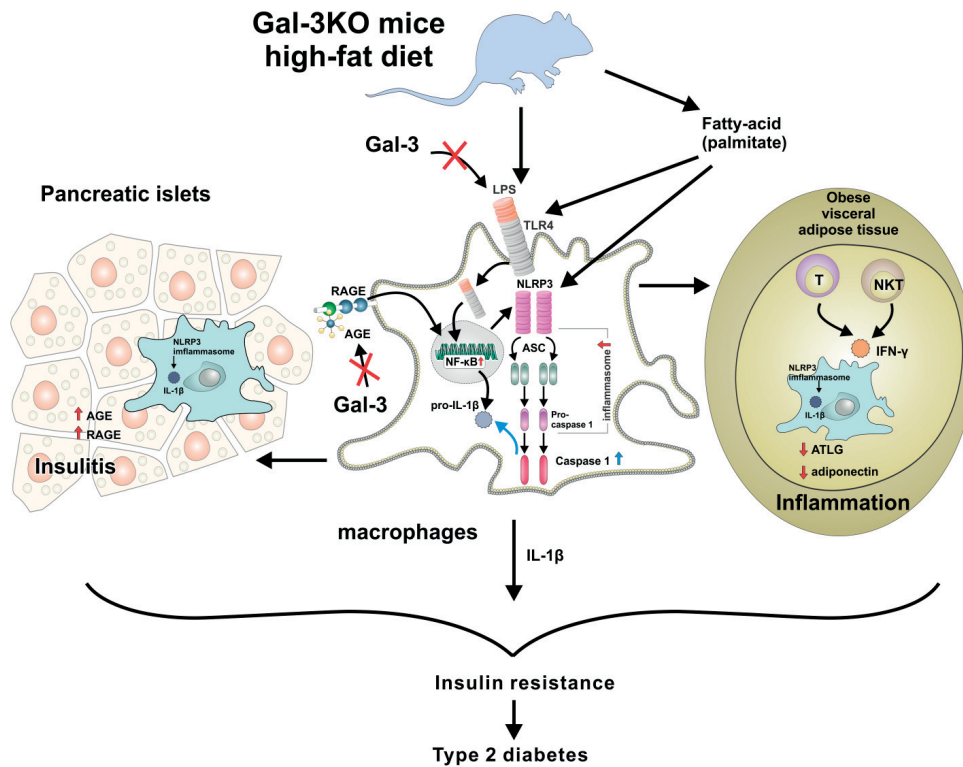
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Figure 2. Involvement of Galectin-3 in obesity and type 2 diabetes

Galectin-3 deficient mice develop accelerated obesity and increased adipose mass, dysregulated glucose metabolism and enhanced inflammation in adipose tissue and pancreatic islets when placed on high-fat diet. Galectin-3 acts as a scavenger molecule for advanced glycation end-products (AGE) and binds lipopolysaccharide (LPS). In the absence of Gal-3, AGE bind to receptor for advanced glycation end-products (RAGE) and gut microbiota derived LPS binds to TLR4 to promote activation of the NFκB pathway in macrophages, leading to secretion of proinflammatory cytokines. LPS also upregulates the NLRP3 inflammasome which, when activated by exogenous danger signals such as saturated fatty acids (palmitate) from a high-fat diet, triggers release of IL-1β, that in turn deregulates insulin signaling and potentially leads to insulin resistance. Enhanced expression of the NLRP3 inflammasome in adipose-tissue macrophages during an obese state in Gal-3 KO mice is associated with activation of T and NKT cells, including production of IFN-γ in adipose tissue which promotes further macrophage activation and systemic inflammation. Obese adipose tissue in Gal-3 KO mice is characterized by decreased expression of adipose tissue triglyceride lipase (ATGL) and adiponectin. Pancreatic islets of obese Gal-3 KO mice are infiltrated with macrophages that express active IL-1β and exhibit increased deposition of AGE and upregulated RAGE. The increase of systemic IL-1β levels and a decrease of anti-inflammatory IL-10 and IL-13 levels contribute to metaflammation in obese Gal-3 KO mice, pointing to Gal-3 as an important regulator of diet-induced obesity and type 2 diabetes.

and fatty acids and inhibits lipolysis (28). Through secretion of adipokines, cytokines and hormones, mature adipocytes contribute to maintaining overall energy balance. During obesity adipocytes become dysfunctional and adipose tissue is infiltrated by pro-inflammatory CD11c+ macrophages and other leukocytes that produce pro-inflammatory cytokines which, among other things, interfere with insulin signaling, while expression of the protective adipokine adiponectin is reduced (29). Enhanced release of fatty acids and inflammatory cytokines leads to development of low-grade systemic inflammation, termed metaflammation, in overweight/obese subjects (30,31).

Increased serum and monocyte-associated levels of Gal-3 are present in obese and T2D subjects and experimental animals (32-35). In obese subjects, circulating levels of Gal-3 positively correlate with serum leptin, resistin, IL-6, and age (35), while in the general population they positively correlate with blood pressure, serum lipids, renal function and age (32).

Both human and murine white adipose tissue expresses Gal-3, with higher levels present in the stromovascular fraction (SVF) compared to mature adipocytes (33,36). Obesity leads to progressive increase of Gal-3 expression particularly in visceral (VAT), but also in subcutaneous (SAT), adipose tissue in mice (33,36). Higher expression of Gal-3 in VAT compared to SAT is also observed in humans (35), although how adipose tissue levels of Gal-3 are regulated during obesity in humans remains to be elucidated. Regulation of Gal-3 during obesity in mice is leptin-independent, with proinflammatory CD11c+ macrophages being the main producers of this galectin (33). The anti-diabetic, PPARγ activators thiazolidinediones (TZD) stimulate adipocyte differentiation, induce adiponectin, decrease adipocyte size and increase insulin sensitivity (37). Administration of the TZD rosiglitazone decreases Gal-3 expression in VAT of HFD-fed mice, with no change in circulating levels, thus pointing to differential regulation and/or release of Gal3 by different tissues and cell types (33). The inhibiting effect of TZD on adipose Gal-3 ex-

pression are likely secondary to their adiponectin-inducing properties (37), since adiponectin directly suppresses Gal-3 expression in monocytes and adipocytes (34,35).

Gal-3 KO mice develop accelerated obesity and significantly increased adipose mass, with higher leptin levels, when placed on high-fat diet (HFD) (38,39). The increase in adiposity is not related to increased food intake and the difference in body weight between the two genotypes is already observed after three weeks of HFD. Despite markedly increased adiposity, Gal-3 KO mice have only a non-significant trend towards larger adipocytes, possibly due to reduced factors involved in adipogenesis, such as PPARγ (38). Incubation of preadipocytes with recombinant Gal-3 stimulates proliferation of preadipocytes *in vitro* through the CRD (36). However, whether Gal-3 directly affects adipogenesis in vivo remains to be addressed. Reduced lipolysis may also contribute to development of obesity in Gal-3 KO mice, as significantly reduced expression of adipose tissue triglyceride lipase, the rate-limiting enzyme in lipolytic pathways, is present in Gal-3 KO mice compared with diet-matched groups (38). A possible direct role for Gal-3 in modulating adipocyte lipolysis has not yet been elucidated.

A two-way cross-talk likely exists between Gal-3 and adiponectin (Fig. 2). In fact, as mentioned above, adiponectin suppresses Gal-3 production (34,35), while both lean and obese Gal-3 KO mice have significantly reduced mRNA expression of adiponectin in VAT, and their adipose tissue cultures *ex vivo* produce lower amounts of adiponectin (38). Although neither circulating nor monocyte-derived Gal-3 correlates with circulating levels of adiponectin in humans (34,35), whether Gal-3 and adiponectin reciprocally regulate each other in adipose tissue remains to be investigated.

In summary, Gal-3 KO mice fed HFD develop accelerated obesity associated with changes of biomarkers of adipose tissue metabolism, pointing to a role of Gal-3 in adipose tissue remodeling and metabolism during obesity.

Galectin-3 regulates inflammatory responses in adipose tissue

Under healthy nutrient intake, the immune microenvironment in adipose tissue adopts a regulatory phenotype that actively maintains high adipocyte insulin sensitivity. This is characterized by the presence of adipose tissue-associated T regulatory cells (Tregs), Type 2 T helper (Th) cells, alternatively activated macrophages and high levels of the anti-inflammatory cytokine IL-10 (40). However, chronic overnutrition results in persistent cellular stress that leads to an increase in the number of proinflammatory adipose tissue leukocytes that establish inflammation and contribute to development of insulin resistance (41,42). Adipose tissue in obese Gal-3 KO mice has increased percentages of T lymphocytes and NKT cells expressing interferon (IFN) γ, with significantly reduced adipose tissue and splenic Tregs compared to WT mice (39). Feed-

ing a HFD also significantly increases CD4+PD1+ cells in VAT and spleen of Gal-3 KO mice, suggesting that activation of T cells is increased in the absence of Gal-3, possibly due to enhanced TCR-mediated signaling (43). This is accompanied by the increase of adipose tissue F4/80+CD11c+CD206+ macrophages and F4/80+CD11b+CD11c+ bone marrow-derived cells and markedly reduced alternatively activated M2 macrophages in obese Gal-3 KO mice (39), in agreement with previous studies demonstrating that Gal-3 is an important factor in modulation of M1/M2 polarization (44).

The NLRP3 inflammasome, a multimolecular complex that catalytically activates caspase-1 causing the release of IL-1β, IL-18 and, through a distinct mechanism, IL-1α, participates in sensing metabolic danger molecules (45). Visceral adipose tissue of obese Gal-3 KO mice has increased percentages of macrophages expressing NLRP3 inflammasome and IL-1β (39). Increased protein expression of NLRP3 inflammasome and active caspase-1, together with increased NF-κB activation, are observed in VAT from obese Gal-3 KO mice (39) (Fig. 2). Moreover, Gal-3-deficient peritoneal macrophages exhibit higher caspase-1 activity and secrete higher amounts of caspase-1-dependent IL-1β in response to stimulation with endotoxin and/or saturated fatty acids compared with cells obtained from WT mice. Silencing the NLRP3 inflammasome attenuates IL-1β production by Gal-3 KO macrophages, suggesting that Gal-3-deficient cells have enhanced NLRP3 inflammasome activation (39). Galectin-3-deficient peritoneal macrophages also produce increased amounts of IL-1β and IL-6 upon stimulation with endotoxin *in vitro*, possibly as a result of the inhibitory effect of Gal-3 when it binds to endotoxin (12). Furthermore, expression of IL-6 and TNFα in VAT of lean and obese Gal-3 KO mice is significantly increased than in respective WT controls (38). Gal-3 KO mice also develop age-related systemic inflammation, irrespective of diet, evidenced by a significant elevation in circulating levels and hepatic mRNA expression of acute-phase proteins, elevation of serum IL-1β and IL-6, with significantly reduced IL-10 and IL-13, as well as hematological alterations, compared to diet-matched WT controls (38,39). Thus, Gal-3 contributes to control excessive activation of NFκB, the NLRP3 inflammasome and downstream inflammation by endotoxin and free fatty acids, most likely through the TLR4 signaling pathway that has been linked to development of insulin resistance and regulation of NLRP3 inflammasome expression (46-48). Collectively, the amplified obesity-induced inflammation of Gal-3 KO mice suggests a regulatory and protective role for Gal-3 in the development of metaflammation.

Galectin-3 and glucose metabolism

Subjects with T2D have elevated circulating levels of Gal-3 (35,49). However, whereas a negative correlation between Gal-3 and glycated hemoglobin (HbA1c) is observed in overweight/obese Caucasian diabetics (35), a positive correlation between Gal-3, HbA1c and vascu-

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lar complications is observed in a population of normal-weight Asian T2D subjects (49). Therefore, whether obesity and/or ethnicity modulate production of Gal3 in T2D remains to be clarified. Monocyte-associated Gal-3 levels are also elevated in overweight/obese subjects with T2D, with a blunted effect of AMPK-activating compounds on Gal-3 production (34).

Gal-3 deficiency in mice leads to dysregulated glucose metabolism, as reflected by the presence of hyperglycemia and impaired glucose tolerance, already noticeable in young Gal-3 KO mice on chow diet and more pronounced with older mice on HFD developing metaflammation (38). The chronic elevation of glucose levels is confirmed by increased levels of HbA1c, hyperinsulinemia and insulin resistance (39). However, expression of gluconeogenic enzymes in the liver and of Glut1 in VAT are not altered in Gal-3 KO mice, suggesting the gluconeogenic response in the liver is not enhanced and insulin-independent disposal of glucose to adipose tissue is not affected in the absence of Gal3 (38). Treatment with antibiotics leads to normalization of hyperglycemia in Gal-3 KO mice, a result that points to the potential role of the microbiota in modulating glucose metabolism, possibly through pattern recognition receptors (38).

Galectin-3 and the pancreas

Overnutrition-related metabolic triggers such as lipotoxicity and glucotoxicity, oxidative stress, endoplasmic reticulum stress, and perturbed autophagy induce inflammatory responses in pancreatic islets, characterized by accumulation of macrophages, enhanced or reduced insulin secretion and β cells apoptosis during T2D progression (50,51).

Obese Gal-3 KO mice exhibit severe insulitis, also present in a proportion of islets in lean Gal-3 KO mice, compared to their respective WT controls (39). In WT mice HFD upregulates Gal-3 protein within pancreatic islets (39). Enhanced expression of Gal-3 protects rat pancreatic β-cells from the cytotoxic effect of IL-1β (52), and Gal-3 is highly expressed in islet endothelial cells in obesity-induced diabetes in mice (53), but its exact role in diabetes progression is poorly understood. Type 2 diabetes may be classified as an autoinflammatory disease with a central role for NLRP3-ASC inflammasome–mediated IL-1β production (54). Increased expression of ASC, mature caspase-1 and active NFκB in pancreatic tissue of obese Gal-3 KO mice compared to WT controls suggests that Gal-3 may be an important player in the pathogenesis of T2D (39). Moreover, islets of obese Gal-3 KO mice have elevated deposition of AGE and increased RAGE expression, which could be an additional mechanism for NFκB activation and IL-1β secretion within islets. Under an inflammatory milieu, ablation or pharmacological inhibition of Gal-3 prevents apoptosis of β cells exposed to proinflammatory cytokines (55), suggesting that endogenous Gal-3 may act to protect β cells from inflammatory stimuli.

Concluding remarks and future perspectives

In conclusion, Gal-3 plays an important role in regulation of adiposity and glucose metabolism in mice. Gal-3 KO mice develop accelerated obesity, metaflammation and systemic inflammation as animals age, which is more pronounced in the presence of metabolic stress induced by HFD.

Future studies will help to elucidate the role of Gal-3 in other metabolic tissues in the course of diet-induced obesity or aging. In particular, clarifying the mechanisms for the protective role of Gal-3 in pancreatic islets in the course of obesity would be of great importance. Obesity, diabetes, heart failure and other diseases associated with inflammation in humans are associated with elevated levels of Gal-3 and further studies are needed to better understand the role of Gal-3 in these conditions, especially in the light of current development of pharmacological inhibitors of Gal-3 for treatment of cancer and fibrosis.

Acknowledgments

REFERENCES

1. Osborn O, Olefsky JM: The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med 2012, 18:363-374.

2. Zhu W, Sano H, Nagai R, Fukuhara K, Miyazaki A, Horiuchi S: The role of galectin-3 in endocytosis of advanced glycation end products and modified low density lipoproteins. Biochem Biophys Res Commun 2001, 280:1183-1188.

3. Hattasch R, Spethmann S, de Boer RA, Ruifrok WP, Schattke S, Wagner M, Schroeckh S, Durmus T, Schimke I, Sanad W, et al.: Galectin-3 increase in endurance athletes. Eur J Prev Cardiol 2013.

4. Radosavljevic G, Jovanovic I, Majstorovic I, Mitrovic M, Lisnic VJ, Arsenijevic N, Jonjic S, Lukic ML: Deletion of galectin-3 in the host attenuates metastasis of murine melanoma by modulating tumor adhesion and NK cell activity. Clin Exp Metastasis 2011, 28:451-462.

5. McCullough PA, Olobatoke A, Vanhecke TE: Galectin-3: a novel blood test for the evaluation and management of patients with heart failure. Rev Cardiovasc Med 2011, 12:200-210.

6. Dragomir AC, Sun R, Choi H, Laskin JD, Laskin DL: Role of galectin-3 in classical and alternative macrophage activation in the liver following acetaminophen intoxication. J Immunol 2012, 189:5934-5941.

7. Hsu DK, Yang RY, Pan Z, Yu L, Salomon DR, Fung-Leung WP, Liu FT: Targeted disruption of the galectin-3 gene results in attenuated peritoneal inflammatory responses. Am J Pathol 2000, 156:1073-1083.

8. Jiang HR, Al Rasebi Z, Mensah-Brown E, Shahin A, Xu D, Goodyear CS, Fukada SY, Liu FT, Liew FY, Lukic ML: Galectin-3 deficiency reduces the severity of experimental autoimmune encephalomyelitis. J Immunol 2009, 182:1167-1173.

9. Mensah-Brown EP, Al Rabesi Z, Shahin A, Al Shamsi M, Arsenijevic N, Hsu DK, Liu FT, Lukic ML: Targeted disruption of the galectin-3 gene results in decreased susceptibility to multiple low dose streptozotocin-induced diabetes in mice. Clin Immunol 2009, 130:83-88.

10. Volarevic V, Milovanovic M, Ljujic B, Pejnovic N, Arsenijevic N, Nilsson U, Leffler H, Lukic ML: Galectin-3 deficiency prevents concanavalin A-induced hepatitis in mice. Hepatology 2012, 55:1954-1964.

11. Mishra BB, Li Q, Steichen AL, Binstock BJ, Metzger DW, Teale JM, Sharma J: Galectin-3 functions as an alarmin: pathogenic role for sepsis development in murine respiratory tularemia. PLoS One 2013, 8:e59616.

12. Li Y, Komai-Koma M, Gilchrist DS, Hsu DK, Liu FT, Springall T, Xu D: Galectin-3 is a negative regulator of lipopolysaccharide-mediated inflammation. J Immunol 2008, 181:2781-2789.

13. Iacobini C, Amadio L, Oddi G, Ricci C, Barsotti P, Missori S, Sorcini M, Di Mario U, Pricci F, Pugliese G: Role of galectin-3 in diabetic nephropathy. J Am Soc Nephrol 2003, 14:S264-270.

14. Pugliese G, Pricci F, Iacobini C, Leto G, Amadio L, Barsotti P, Frigeri L, Hsu DK, Vlassara H, Liu FT, et al.: Accelerated diabetic glomerulopathy in galectin-3/AGE receptor 3 knockout mice. FASEB J 2001, 15:2471-2479.

15. Iacobini C, Menini S, Oddi G, Ricci C, Amadio L, Pricci F, Olivieri A, Sorcini M, Di Mario U, Pesce C, et al.: Galectin-3/AGE-receptor 3 knockout mice show accelerated AGE-induced glomerular injury: evidence for a protective role of galectin-3 as an AGE receptor. FASEB J 2004, 18:1773-1775.

16. Iacobini C, Menini S, Ricci C, Scipioni A, Sansoni V, Mazzitelli G, Cordone S, Pesce C, Pugliese F, Pricci F, et al.: Advanced lipoxidation end-products mediate lipid-induced glomerular injury: role of receptor-mediated mechanisms. J Pathol 2009, 218:360-369.

17. Iacobini C, Oddi G, Menini S, Amadio L, Ricci C, Di Pippo C, Sorcini M, Pricci F, Pugliese F, Pugliese G: Development of age-dependent glomerular lesions in galectin-3/AGE-receptor-3 knockout mice. Am J Physiol Renal Physiol 2005, 289:F611-621.

18. Iacobini C, Menini S, Ricci C, Blasetti Fantauzzi C, Scipioni A, Salvi L, Cordone S, Delucchi F, Serino M, Federici M, et al.: Galectin-3 ablation protects mice from diet-induced NASH: a major scavenging role for galectin-3 in liver. J Hepatol 2011, 54:975-983.

19. 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, 23:654-663.

20. Iacobini C, Menini S, Ricci C, Scipioni A, Sansoni V, Cordone S, Taurino M, Serino M, Marano G, Federici M, et al.: Accelerated lipid-induced atherogenesis in galectin-3-deficient mice: role of lipoxidation via receptor-mediated mechanisms. Arterioscler Thromb Vasc Biol 2009, 29:831-836.

21. Nomoto K, Nishida T, Nakanishi Y, Fujimoto M, Takasaki I, Tabuchi Y, Tsuneyama K: Deficiency in galectin-3 promotes hepatic injury in CDAA diet-induced nonalcoholic fatty liver disease. ScientificWorldJournal 2012, 2012:959824.

22. Nomoto K, Tsuneyama K, Abdel Aziz HO, Takahashi H, Murai Y, Cui ZG, Fujimoto M, Kato I, Hiraga K, Hsu DK, et al.: Disrupted galectin-3 causes non-alcoholic fatty liver disease in male mice. J Pathol 2006, 210:469-477.

23. Chung AW, Sieling PA, Schenk M, Teles RM, Krutzik SR, Hsu DK, Liu FT, Sarno EN, Rea TH, Stenger S, et al.: Galectin-3 regulates the innate immune response of human monocytes. J Infect Dis 2013, 207:947-956.

24. Fermin Lee A, Chen HY, Wan L, Wu SY, Yu JS, Huang AC, Miaw SC, Hsu DK, Wu-Hsieh BA, Liu FT: Galectin-3 Modulates Th17 Responses by Regulating Dendritic Cell Cytokines. Am J Pathol 2013.

25. Wu SY, Yu JS, Liu FT, Miaw SC, Wu-Hsieh BA: Galectin-3 negatively regulates dendritic cell production of IL-23/IL-17-axis cytokines in infection by Histoplasma capsulatum. J Immunol 2013, 190:3427-3437.

26. Kavanaugh D, Kane M, Joshi L, Hickey RM: Detection of galectin-3 interaction with commensal bacteria. Appl Environ Microbiol 2013, 79:3507-3510.

27. Quattroni P, Li Y, Lucchesi D, Lucas S, Hood DW, Herrmann M, Gabius HJ, Tang CM, Exley RM: Galectin-3 binds Neisseria meningitidis and increases interaction with phagocytic cells. Cell Microbiol 2012, 14:1657-1675.

28. Gregor MF, Hotamisligil GS: Inflammatory mechanisms in obesity. Annu Rev Immunol 2011, 29:415-445.

29. Rask-Madsen C, Kahn CR: Tissue-specific insulin signaling, metabolic syndrome, and cardiovascular disease. Arterioscler Thromb Vasc Biol 2012, 32:2052-2059.

30. Guilherme A, Virbasius JV, Puri V, Czech MP: Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol 2008, 9:367-377.

31. Haffner SM: Abdominal adiposity and cardiometabolic risk: do we have all the answers? Am J Med 2007, 120:S10-16; discussion S16-17.

32. de Boer RA, van Veldhuisen DJ, Gansevoort RT, Muller Kobold AC, van Gilst WH, Hillege HL, Bakker SJ, van der Harst P: The fibrosis marker galectin-3 and outcome in the general population. J Intern Med 2012, 272:55-64.

33. Rhodes DH, Pini M, Castellanos KJ, Montero-Melendez T, Cooper D, Perretti M, Fantuzzi G: Adipose tissue-specific modulation of galectin expression in lean and obese mice: evidence for regulatory function. Obesity (Silver Spring) 2013, 21:310-319.

34. Weber M, Sporrer D, Weigert J, Wanninger J, Neumeier M, Wurm S, Stogbauer F, Kopp A, Bala M, Schaffler A, et al.: Adiponectin downregulates galectin-3 whose cellular form is elevated whereas its soluble form is reduced in type 2 diabetic monocytes. FEBS Lett 2009, 583:3718-3724.

35. Weigert J, Neumeier M, Wanninger J, Bauer S, Farkas S, Scherer MN, Schnitzbauer A, Schaffler A, Aslanidis C, Scholmerich J, et al.: Serum galectin-3 is elevated in obesity and negatively correlates with glycosylated hemoglobin in type 2 diabetes. J Clin Endocrinol Metab 2010, 95:1404-1411.

36. 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, 15:32-39.

37. Johnson JA, Trasino SE, Ferrante AW, Jr., Vasselli JR: Prolonged decrease of adipocyte size after rosiglitazone treatment in high- and low-fat-fed rats. Obesity (Silver Spring) 2007, 15:2653-2663.

38. Pang J, Rhodes DH, Pini M, Akasheh RT, Castellanos KJ, Cabay RJ, Cooper D, Perretti M, Fantuzzi G: Increased adiposity, dysregulated glucose metabolism and systemic inflammation in Galectin-3 KO mice. PLoS One 2013, 8:e57915.

39. Pejnovic NN, Pantic JM, Jovanovic IP, Radosavljevic GD, Milovanovic MZ, Nikolic IG, Zdravkovic NS, Djukic AL, Arsenijevic NN, Lukic ML: Galectin-3 deficiency accelerates high-fat diet-induced obesity and amplifies inflammation in adipose tissue and pancreatic islets. Diabetes 2013, 62:1932-1944.

40. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, et al.: Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 2009, 15:930-939.

41. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, Otsu M, Hara K, Ueki K, Sugiura S, et al.: CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med 2009, 15:914-920.

42. 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, 112:1796-1808.

43. Chen HY, Fermin A, Vardhana S, Weng IC, Lo KF, Chang EY, Maverakis E, Yang RY, Hsu DK, Dustin ML, et al.: Galectin-3 negatively regulates TCR-mediated CD4+ T-cell activation at the immunological synapse. Proc Natl Acad Sci U S A 2009, 106:14496-14501.

44. MacKinnon AC, Farnworth SL, Hodkinson PS, Henderson NC, Atkinson KM, Leffler H, Nilsson UJ, Haslett C, Forbes SJ, Sethi T: Regulation of alternative macrophage activation by galectin-3. J Immunol 2008, 180:2650-2658.

45. Schroder K, Zhou R, Tschopp J: The NLRP3 inflammasome: a sensor for metabolic danger? Science 2010, 327:296-300.

46. Qiao Y, Wang P, Qi J, Zhang L, Gao C: TLR-induced NF-kappaB activation regulates NLRP3 expression in murine macrophages. FEBS Lett 2012, 586:1022-1026.

47. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS: TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 2006, 116:3015-3025.

48. Song MJ, Kim KH, Yoon JM, Kim JB: Activation of Toll-like receptor 4 is associated with insulin resistance in adipocytes. Biochem Biophys Res Commun 2006, 346:739-745.

49. 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, 126:2109-2115.

50. Donath MY, Shoelson SE: Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 2011, 11:98-107.

51. Odegaard JI, Chawla A: Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science 2013, 339:172-177.

52. Karlsen AE, Storling ZM, Sparre T, Larsen MR, Mahmood A, Storling J, Roepstorff P, Wrzesinski K, Larsen PM, Fey S, et al.: Immune-mediated beta-cell destruction in vitro and in vivo-A pivotal role for galectin-3. Biochem Biophys Res Commun 2006, 344:406-415.

53. Darrow AL, Shohet RV, Maresh JG: Transcriptional analysis of the endothelial response to diabetes reveals a role for galectin-3. Physiol Genomics 2011, 43:1144-1152.

54. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM, Dixit VD: The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med 2011, 17:179-188.

55. Saksida T, Nikolic I, Vujicic M, Nilsson UJ, Leffler H, Lukic ML, Stojanovic I, Stosic-Grujicic S: Galectin-3 deficiency protects pancreatic islet cells from cytokine-triggered apoptosis in vitro. J Cell Physiol 2013, 228:1568-1576.

56. Nachtigal M, Ghaffar A, Mayer EP: Galectin-3 gene inactivation reduces atherosclerotic lesions and adventitial inflammation in ApoE-deficient mice. Am J Pathol 2008, 172:247-255.

57. Fernandes Bertocchi AP, Campanhole G, Wang PH, Goncalves GM, Damiao MJ, Cenedeze MA, Beraldo FC, de Paula Antunes Teixeira V, Dos Reis MA, Mazzali M, et al.: A Role for galectin-3 in renal tissue damage triggered by ischemia and reperfusion injury. Transpl Int 2008, 21:999-1007.

58. Nakanishi Y, Tsuneyama K, Nomoto K, Fujimoto M, Salunga TL, Nakajima T, Miwa S, Murai Y, Hayashi S, Kato I, et al.: Nonalcoholic steatohepatitis and hepatocellular carcinoma in galectin-3 knockout mice. Hepatol Res 2008, 38:1241-1251.