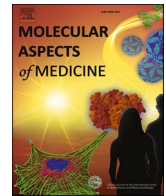




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Galectins in allergic inflammatory diseases

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ABSTRACT

Allergic inflammatory diseases are a global public health concern affecting millions of people. Although there are several potential hypotheses, details regarding their molecular mechanisms are still ambiguous. Recently, a group of β -galactoside-binding proteins, galectins, have been revealed as important factors in altering allergic chronic inflammatory diseases. In this review, we describe the molecular and cellular basis of how galectins modulate inflammatory reactions. We also provide an overview of clinical features related to galectins. Finally, we discuss the potential issues that might lead to misrepresentation of the exact biological functions of galectins.

1. Introduction

The theory of "atopy" was established by Coca and Cooke in 1923 to characterize the phenomenon of allergic hypersensitivity (Coca and Cooke, 1923). Atopy is indicated by distorted immune responses to allergic antigens and elevated serum IgE, which cause clinical diseases based on different anatomic sites. Generally, atopy does not present in infants at birth (Wahn, 2000); however, individuals who suffer from atopy are inclined to develop allergies. Atopic dermatitis, allergic rhinitis, and asthma frequently occur in one person (Rhodes et al., 2001, 2002). In addition, food allergies and allergic conjunctivitis are also prevalent in individuals with atopy (Burks et al., 2012; Rance, 2008; Sicherer and Leung, 2014).

Atopic march depicts a sequence of allergic events followed by atopic dermatitis, food allergy, allergic rhinitis, and asthma (Han et al., 2017). It represents a developmental advancement of atopic diseases. Atopic march is generally initiated with atopic dermatitis in early infancy and its prevalence peaks within 2 years of age (Eller et al., 2010). Most infants develop atopic dermatitis before 6 months (Eller et al., 2010; Kay et al., 1994). Children who develop atopic dermatitis are more susceptible to other atopic diseases than those without atopic dermatitis (Lack et al., 2003; Tsakok et al., 2016). In addition, atopic dermatitis severity and chronicity are related to an increase in the prevalence of atopic

diseases. Approximately, 20% patients with mild atopic dermatitis develop asthma, whereas asthma presents in 60% of patients with severe atopic dermatitis (Lack et al., 2003; Tsakok et al., 2016; von Kobyletzki et al., 2012). Moreover, patients with atopic dermatitis display a 6-fold higher incidence of food allergies than healthy controls. This association increases with age of onset, severity, and chronicity of atopic dermatitis (Tsakok et al., 2016). Atopic diseases such as allergic airway diseases represent a consequential burden to health. Globally, there are approximately 339 million people who suffer from asthma, and this number is expected to continue to increase in the future. The prevalence of atopic dermatitis and allergic rhinitis has also increased progressively in recent decades.

Galectins are a family of β -galactoside-binding proteins that display a consensus sequence in the carbohydrate recognition domain (CRD). A total of 17 different mammalian galectins have been described. Generally, galectins are grouped based on the number of CRDs, either containing one or two CRDs. Galectin-1, 2, 5, 7, 10, 11, 13, 14, 15, 16, and 17 are one-CRD galectins, whereas galectin-4, 6, 8, 9, and 12 are two-CRD galectins, containing two distinct but homologous CRDs. Galectin-3 is different in that it has one CRD and a non-lectin domain composed of proline- and glycine-rich short tandem repeats. Some galectins are widely distributed in different tissues, whereas others are restricted to certain tissues or cell types. Different galectins show

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differential carbohydrate-binding specificities and affinities (Liu and Rabinovich, 2010; Yang and Liu, 2003). Through CRDs, homodimers and heterodimers are frequently discovered, whereas oligomeric galectin-3 is formed by interacting with multivalent carbohydrates.

Galectins can be detected intracellularly and extracellularly; however, they are synthesized without a classical signal sequence (Liu and Rabinovich, 2010; Yang and Liu, 2003). The detailed molecular mechanisms concerning galectin transport across the cell membrane are still unknown. There is no specific cell-surface receptors for galectins, but transmitted signals across cell membranes exist through their interaction with carbohydrate moieties on glycoproteins. The biological activities of recombinant galectins can generally be observed through the interaction between CRDs and carbohydrates on glycoproteins on the cell surfaces or in the extracellular matrix. However, for the most part, added recombinant proteins may or may not represent the endogenous bioactivities of galectins because the concentrations of the recombinant galectins used to demonstrate biological activities might be generally not achievable under physiological or pathological conditions. In addition to extracellular activities, several studies have described the intracellular biological activities of galectins; some of these are not related to carbohydrate binding. Galectins modulate intracellular signaling through direct interactions with signaling molecules (Liu and Rabinovich, 2010; Yang and Liu, 2003). Galectins are known to be engaged in cell adhesion, migration, and growth and involved in the pathogenesis of several diseases, including cancer initiation, progression, and metastasis. Galectins are also involved in the activation and regulation of both innate and adaptive immune responses; hence, they participate in the pathogenesis of autoimmune and allergic diseases. In this review, only studies that are related to functions of endogenous galectins are included, and the focus is on the biological role of galectins in the pathogenesis of allergic diseases.

2. Galectin-1 (Gal-1)

Gal-1 is the first identified galectin and typically functions as a pro-resolving mediator by modulating innate and adaptive immune responses (Sundblad et al., 2017). Gal-1 often functions as a dimer. The homo-dimerization of Gal-1 protects the oxidation of the cysteine residues known to affect its biological activities when oxidized (Stowell et al., 2009). Gal-1 binds to galactose- β 1-N-acetyl-glucosamine (N-acetyl-lactosamine [LacNAc]) groups on N- or O-linked glycans present on various cell surface receptors. Gal-1 can be detected in the immune system in a variety of cells, which include regulatory T cells (Dalotto-Moreno et al., 2013; Garin et al., 2007), activated T and B cells (Fuentes et al., 2004; Zuniga et al., 2001), macrophages (Rabinovich et al., 1996), dendritic cells (Ilarregui et al., 2009; Tesone et al., 2016), and microglia (Starosom et al., 2012). Gal-1 is potentially involved in immune-privileged regulation, identified in the placenta (Blois et al., 2007; Ramhorst et al., 2012), testis (Dettin et al., 2003; Perez et al., 2015), and eye (Ridano et al., 2017). The level of Gal-1 is either upregulated or downregulated in various inflammatory scenarios such as microbial infection (Davicino et al., 2017; Poncini et al., 2015; Suryawanshi et al., 2013), autoimmunity (Santucci et al., 2003), cancer (Martinez-Bosch and Navarro, 2020), endometriosis (Baston et al., 2014; Vergetaki et al., 2014), neurodegenerative diseases (Starosom et al., 2012), myocardial infarction (Al-Salam and Hashmi, 2014; Seropian et al., 2013), and allergic inflammatory conditions (Liu, 2005).

Although Gal-1 has been considered an anti-inflammatory and pro-resolving protein, only a few reports have focused on the function of endogenous Gal-1 in the pathogenesis of allergic inflammation (Rao et al., 2017). Most of these studies stated that Gal-1 might be involved indirectly by maintaining T-cell homeostasis through the induction of apoptosis in activated T cells, which modulates immune reactions associated with allergic inflammation. In addition to the effects on activated T cells, Gal-1 can also adjust inflammation by inducing the expression of interleukin (IL)-10 via regulatory T cells (Stowell et al.,

2008; van der Leij et al., 2007). Ge et al. showed that Gal-1 is associated with allergic airway inflammation. They demonstrated that Gal-1-knockout mice exhibit more severe airway inflammation characterized by higher T cell and eosinophil infiltration (Ge et al., 2016). The evaluation of airway hyperresponsiveness revealed increased pulmonary resistance in Gal-1-knockout mice. Moreover, the inflammatory cytokine tumor necrosis factor alpha (TNF α) was found to be significantly upregulated in the bronchoalveolar lavage fluid (BALF) in Gal-1-knockout mice with allergic airway inflammation as compared to that in wild-type mice (Ge et al., 2016). They also found a low number of eosinophils in lungs of the wild-type mice with most eosinophils attached to the endothelium of blood vessels, whereas in Gal-1-knockout mice, more eosinophils were found in lungs with fewer cells attached to the endothelium. The results suggest that Gal-1 might be involved in eosinophil trafficking (Ge et al., 2016). Some studies suggested that the extracellular lectin-binding activities of Gal-1 are responsible for altering eosinophil trafficking through direct interactions with cell surface glycoproteins, which further modify actin polymerization (Delbrouck et al., 2002; Rao et al., 2017). Actin polymerization is critical for cell adhesion and migration. However, most studies did not investigate the potential influence of Gal-1 on chemokines or adhesion molecule levels in both eosinophils and endothelial cells. Tissue- or cell-specific Gal-1-knockout mice are more suitable to identify the actual role of Gal-1 in blood-cell trafficking. Clinically, Gal-1 levels are lower in sputum macrophages from patients with asthma than in those from healthy donors (Sanchez-Cuellar et al., 2012). These results support the notion that downregulating Gal-1 aggravates asthma (summarized in Fig. 1).

3. Galectin-3 (Gal-3)

Gal-3 was first identified in thioglycollate-elicited murine macrophages as MAC-2 (Ho and Springer, 1982). It was subsequently detected in various types of cells and has been known to have different names, including Lectin L-29 (Cerra et al., 1985), carbohydrate binding protein (CBP)-35 (Roff and Wang, 1983), L-34 (Lotan et al., 1989), CBP-30 (Sato and Hughes, 1992), and IgE-binding protein (Albrandt et al., 1987). Gal-3 is considered a modulator/mediator of allergic immune responses based on its interaction with IgE. Gal-3 binds lactose-containing glycans such as Gal (β 1-4)Glc β and LacNAc saccharides. The addition of fucose to LacNAc considerably increases the binding affinity (Horlacher et al., 2010).

Gal-3 is ubiquitously expressed in most tissues and cells, including respiratory epithelial cells, alveolar cells, mast cells, neutrophils, monocytes/macrophages, eosinophils, and T cells (Casals et al., 2018; Liu, 2000). The biological functions of Gal-3 have been extensively studied. It is associated with the pathogenesis of various diseases, including several different cancer types, metabolic diseases, cardiac diseases, liver diseases, autoimmune diseases, and allergic diseases (Wan and Liu, 2016). Most studies suggested a proinflammatory role of Gal-3 (Chen et al., 2006; Forsman et al., 2011; Hsu et al., 2000, 2009; Zuberi et al., 2004).

The association between Gal-3 and allergic inflammation was revealed based on its IgE-binding activities. Gal-3 binds to IgE through the sialylation of IgE oligosaccharides, which results in differential binding activities with different polyclonal IgEs isolated from patients with hyper-IgE syndrome or atopic dermatitis (Robertson and Liu, 1991). Gal-3 is associated with neutrophil activation induced by IgE; neutrophil respiratory burst is inhibited upon treatment with anti-Gal3 monoclonal antibodies (Truong et al., 1993). The production of IgE by B cells isolated from patients with atopic eczema/dermatitis syndrome (AEDS) can be induced by AEDS polymorphonuclear leukocytes and not cells from non-atopic individuals. Further, activated IgE production can be inhibited by lactose and anti-Gal3 antibodies (Kimata, 2002).

Gal-3 is also involved in mast cell biology; ablating Gal-3 lowers passive cutaneous anaphylaxis reactions as compared to those in wild-

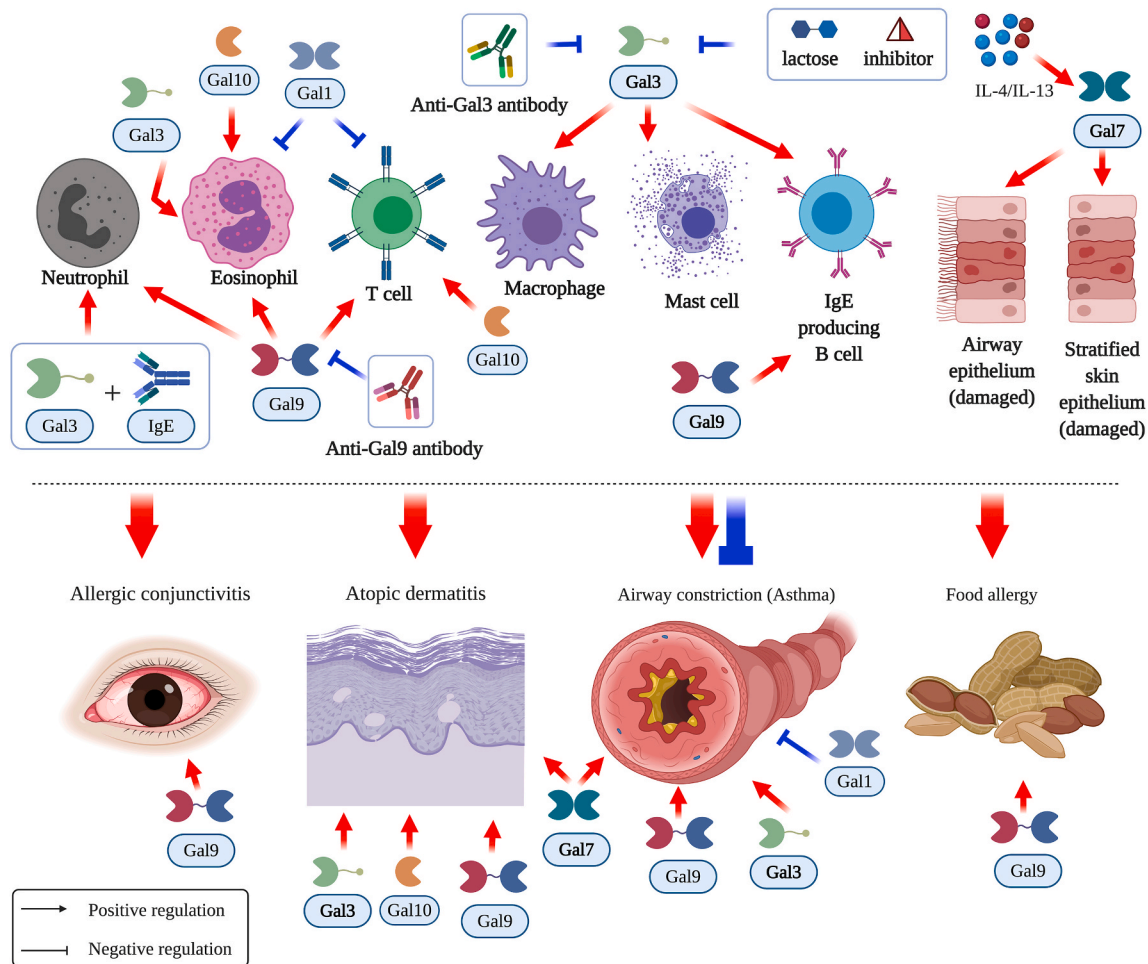


Fig. 1. Galectins control a wide range of cells involved in the allergic inflammatory diseases. By modulating the biological activities of the cells, galectins may influence the development and course of allergic diseases. Clinical studies or research articles performed in mice deleting individual members of the galectin family, or by gene delivery in wild-type mice, have disclosed immunoregulatory activities of galectins in allergic circumstances. Specifically, galectins may selectively alter the survival, activation or cytokine production by neutrophils, eosinophils, T cells, macrophages, mast cells, B cells or epithelial cells. Galectins can regulate the polarization of T cells and macrophages resulting in modulation of the balance between pro-inflammatory and anti-inflammatory activities in allergy settings. In addition, galectins can regulate the production of IgE which is a major contributor to allergic inflammation. Through these various mechanisms, galectins are involved in the pathogenesis of allergic conjunctivitis, atopic dermatitis, asthma and food allergy. The allergic inflammation may be modulated with anti-galectin antibodies or inhibitors.

type mice. Gal-3-deficient bone marrow-derived mast cells express low amounts of histamine and IL-4 when activated by the FcεRI cross-linkage (Chen et al., 2006). In an ovalbumin (OVA)-induced asthma mice model, OVA-sensitized Gal-3-deficient mice showed fewer eosinophils in the BALF as compared to that wild-type mice treated with OVA. Gal-3 protein levels in BALF are increased in wild-type mice challenged with OVA (Ge et al., 2010; Zuberi et al., 2004). These results suggested a role of Gal-3 in eosinophil trafficking and were supported by the fact that eosinophils isolated from allergic donors (with higher expression of Gal-3) exhibit stronger rolling and adhesion to vascular cell adhesion molecule 1 (VCAM-1) as compared to eosinophils from healthy individuals. The rolling and adhesion can be reduced by an anti-Gal3 antibody and lactose. Gal-3 is located on the cell surface and interacts with α4β1. Lactose blocks the interaction between Gal-3 and α4β1, which suggests that the carbohydrate-binding activities of Gal-3 are involved in this process (Rao et al., 2007). The importance of Gal-3 in eosinophil trafficking was further supported by experiments in Gal-3-deficient mice. Gal-3-deficient mice exhibit fewer eosinophils in the BALF and fewer eosinophils infiltrate the lungs of OVA-challenged Gal-3-deficient mice compared to numbers in wild-type mice (Ge et al., 2010). Bone marrow-derived eosinophils from Gal-3-deficient

mice show diminishing rolling on VCAM-1 and adhesion with intercellular adhesion molecule 1 (ICAM-1) compared to those from wild-type mice (Ge et al., 2013). Eosinophil migration towards eotaxin-1 is also reduced for Gal-3-deficient eosinophils and is not inhibited by lactose as compared to that in wild-type eosinophils. These results indicate that Gal-3 functions intracellularly to alter cell motility (Ge et al., 2013).

Macrophages isolated from Gal-3-deficient mice were found to exhibit a significantly lower level of NF-κB response, which leads to a lower inflammatory response (Hsu et al., 2000). Gal-3 is crucial for phagocytotic activities of macrophages, as evidenced by Gal-3-deficient macrophages exhibiting attenuated IgG-mediated phagocytosis (Sano et al., 2003). In an OVA-induced mouse asthma model, macrophages were found to be the most abundant cell types in the BALF of OVA-challenged wild-type mice as compared to that in OVA-administered Gal-3-deficient mice (Zuberi et al., 2004). The plasticity of macrophages results in a differential outcome for asthma pathogenesis. Some studies reported protective effects against inflammation and lung homeostasis maintenance (Moreira et al., 2010; Robbe et al., 2015); however, some reports demonstrated that macrophages promote the severity of asthma (Bourdonnay et al., 2015; Zaslona et al., 2014). There are two different polarization phenotypes of macrophages,

proinflammatory M1 macrophages and pro-repair M2 macrophages. M1 macrophages can be induced by treatment with interferon gamma (IFN γ), whereas IL-4 promotes M2 macrophage polarization (Draijer et al., 2018). M2 macrophages exhibit lower phagocytic activities than M1 macrophages. Reducing the level of Gal-3 enhances macrophage M2 polarization and ameliorates airway hyperresponsiveness and inflammation (Li et al., 2020).

Gal-3 also plays a role in T-cell polarization. In an atopic dermatitis mouse model, Gal-3 ablation significantly reduces thickening of the epidermis, lowers infiltrating eosinophils, and decreases serum IgE levels compared to wild-type mice (Saegusa et al., 2009). Deletion of Gal-3 promotes Th1 polarization, evidenced by higher IL-4 and lower IFN- γ in sera; IL-12 was found to be secreted by splenocytes and Th1 polarization is enhanced in Gal-3-knockout dendritic cells. The effect was further confirmed by adoptive T-cell transfer from Gal-3-deficient mice to wild-type mice, which significantly lowered the Th2 response and reduced dermatitis (Saegusa et al., 2009). IgE secretion by B cells is enhanced by the polymorphonuclear leukocytes of patients with atopic eczema/dermatitis but not by those of non-atopic individuals. Gal-3 is involved in activated IgE production, as evidenced by the reduction in IgE levels upon treatment with lactose and anti-Gal-3 antibodies (Kimata, 2002). Gal-3 is also involved in IgE production activated by specific allergens. B cells were previously obtained from patients with atopic dermatitis allergic to Japanese cedar pollen, and IgE production was found to be inhibited when B cells were treated with lactose or anti-Gal-3 antibodies (Kimata, 2007). The biological functions of Gal-3 are summarized in Fig. 1.

In contrast to the proinflammatory role of Gal-3, Gal-3 overexpression in the lung via the orotracheal instillation Gal-3 plasmid DNA significantly reduces eosinophil infiltration and re-establishes pulmonary function in both acute and chronic airway inflammation mouse models (del Pozo et al., 2002; Lopez et al., 2006). Gal-3 overexpression inhibits suppressor levels of cytokine signaling 1 and 3, which are two signaling molecules that regulate the Th1–Th2 balance (Lopez et al., 2011). The exact molecular mechanisms regarding the difference in the biological effects of endogenous galectin-3 are unknown. Gal-3 overexpression leads to apoptosis in T cells, macrophages, and dendritic cells, which are important in allergy development. Further, conditional Gal-3 knockout in the lung should be used to confirm the possible use of the Gal-3 plasmid as a therapeutic tool for asthma.

4. Galectin-7 (Gal-7)

Gal-7 can be detected in stratified epithelia (Madsen et al., 1995; Magnaldo et al., 1995), hair follicles (Magnaldo et al., 1998), thymic Hassall's corpuscles (Magnaldo et al., 1998), sebaceous glands (Nio-Kobayashi, 2017), and myoepithelial cells from mammary epithelia (Jones et al., 2004). P53, UVB light exposure, and TNF α treatment induce Gal-7 expression, which is downregulated by retinoic acid. Its level is also decreased in SV40-transformed epithelial cells and squamous cell carcinoma (Advedissian et al., 2017; Nio-Kobayashi, 2017). Gal-7 exhibits conserved carbohydrate binding residues as compared to Gal-1. However, with its short CRD loop structure, Gal-7 shows different binding specificity compared to Gal-1. Gal-1 primarily interacts with oligosaccharides with non-reducing terminal LacNAc residues. Gal-7 binds to both non-reducing terminal LacNAc residues and internal LacNAc residues (Brewer, 2002).

As Gal-7 is found in various stratified epithelial cells, studies related to allergic inflammation have primarily focused on the barrier functions of the epithelium. Gal-7 is overexpressed in the stratum corneum or atopic dermatitis (AD) lesional epidermis (Niijima et al., 2016; Umayahara et al., 2020). The serum Gal-7 level is significantly higher in patients with AD than in healthy individuals. Th2 cytokines, IL4/IL13, promote Gal-7 expression in normal human epidermal keratinocytes, which is inhibited by STAT6 (Umayahara et al., 2020). In a 3D-reconstructed epidermis, downregulating Gal-7 was found to protect against

the disruption of cell-to-cell and cell-to-extracellular matrix adhesion induced by IL-4/IL-13 (Umayahara et al., 2020).

Gal-7 has also been linked to the barrier integrity of the airway epithelium, which is pseudostratified. In Gal-7 transgenic mice with this galectin being overexpressed in the airway among other organs and tissues, impaired airway epithelial barrier function and enhanced airway hyperresponsiveness were noted. The levels of tight-junction related protein zonula occludens-1 and E-cadherin are downregulated in Gal-7 transgenic mice. Gal-7 enhances bronchial epithelial detachment and apoptosis by releasing mitochondrial cytochrome c, increasing the caspase-3 level, and boosting JNK1 activation (Tian et al., 2020). The biological functions of Gal-7 are summarized in Fig. 1.

5. Galectin-9

Gal-9 was initially characterized as a transmembrane transporter that maintains urate homeostasis in rat kidneys (Leal-Pinto et al., 1997), as an autoantigen identified from Hodgkin's disease tissue (Tureci et al., 1997), or as ecalectin that functions as an eosinophil chemoattractant (Matsumoto et al., 1998). Gal-9 can be detected in various tissues, including the lung, stomach, intestine, bone marrow, spleen, thymus, and lymph nodes (Hirashima, 2000). The N-terminal and C-terminal CRDs are covalently connected by a short linker peptide. The length of the linker peptide is determined by exon 5 and 6; hence, alternative splicing of exon 5 and 6 would produce a different linker peptide. There are three different lengths of the linker, which are 14, 26, and 56 amino acids long (Sato et al., 2002). Gal-9 isoforms generated by alternative splicing show differential binding affinity and avidity for glycan units (John and Mishra, 2016). Different biological activities were also noted among various Gal-9 isoforms (Aanhane et al., 2018; Heusschen et al., 2014). Full-length Gal-9 is often named Gal-9L (56 amino acids linker), Gal-9 without exon 5 is designated as Gal-9M (26 amino acids linker), and that without both exon 5 and 6 is identified as Gal-9S (14 amino acids linker). Carbohydrate-binding activities are essential for the eosinophil chemoattractant activity of Gal-9. There is no difference in eosinophil chemoattract activity among Gal-9L, Gal-9M, and Gal-9S, which suggests that the linker length is not related to this biological effect (Sato et al., 2002).

In a guinea pig asthma model, Gal-9 levels were elevated in the bronchial epithelium and interstitial macrophages in sensitized rats as compared to those in non-sensitized controls. Eosinophil infiltration in BALF also increases in challenged rats as compared to that in non-challenged animals (Yamamoto et al., 2007). Consistently, in an asthma mouse model, the Gal-9 level increased in the OVA-challenged lung and BALF lymphocytes, eosinophils, and granulocytes. The number of eosinophils was also higher in OVA-challenged BALF than in that from mice sensitized with phosphate-buffered saline (Sziks et al., 2010). Gal-9 is also involved in the development of experimental allergic conjunctivitis (EAC) in mice. There is no significant beneficial effect against EAC in mice treated with anti-Gal-9 monoclonal antibodies. Spleen cells were isolated from EAC mice and subsequently incubated with allergen and anti-Gal-9 antibodies for 3 d, and the cells were intraperitoneally injected into naïve mice. Recipient mice were challenged with allergen in eye drops after 4 d of cell transfer. A significantly lower eosinophil infiltration was revealed in conjunctiva compared to that in mice injected with normal rat IgG-treated splenocytes (Fukushima et al., 2008). The results suggested that Gal-9 modulates the allergic reaction, not only as an eosinophil chemoattractant but also by altering the biological function of lymphocytes. In addition to Gal-1, Gal-9 was found to be downregulated in sputum macrophages from patients with asthma compared to those from healthy donors (Sanchez-Cuellar et al., 2012).

Gal-9 is significantly increased in intestinal epithelial cells (IECs) of duodenal biopsies from patients with food allergy. The upregulation of Gal-9 in IECs is induced by mast cell-secreted tryptase. In a mouse food allergy model, treatment with anti-Gal-9 monoclonal antibody

significantly inhibits hypersensitivity status. Significantly lower OVA-specific IgE and IL-4 were also identified. Mast cells and eosinophils in jejunal tissue were also found to be reduced (Chen et al., 2011). In addition to that in food allergy, serum Gal-9 was significantly elevated in patients with atopic dermatitis as compared to control individuals, and the level correlates with disease severity (Nakajima et al., 2015; Nofal et al., 2019). Gal-9 is also increased in the skin lesions of patients with atopic dermatitis (Farag et al., 2020; Nakajima et al., 2015) and was found to be expressed in epidermal keratinocytes and mast cells (Nakajima et al., 2015). Gal-9 level is decreased in patients with moderate or severe atopic dermatitis when they are treated with topical corticosteroids, topical tacrolimus, or oral anti-histamine drugs (Nakajima et al., 2015). These reports suggest that Gal-9 overexpression might enhance allergic inflammatory reactions.

However, some studies indicated that upregulating Gal-9 has a protective effect against allergic inflammation. Gal-9 in serum and IECs is increased in mice fed galacto- and fructo-oligosaccharides (prebiotics) or probiotics (*Bifidobacterium breve* M-16V), and the level of Gal-9 is inversely correlated with mast cell degranulation in vivo (de Kivit et al., 2012). Oral administration of fucoidan, a sulfated polysaccharide from *Saccharina japonica*, inhibits passive cutaneous anaphylaxis reactions (Tanino et al., 2016) and OVA-induced anaphylaxis (Mizuno et al., 2020) by inducing Gal-9 expression. Further, the antiallergic activities of fucoidan are abolished with the intravenous administration of an anti-Gal-9 antibody (van Esch et al., 2016). These results suggest that Gal-9 overexpression or recombinant Gal-9 might exhibit potential therapeutic efficacy against allergic inflammation reactions.

Gal-9 has been shown to be involved in amplifying the humoral immune response by interacting with IgD and CD44. Some B cells differentiate into IgD-producing plasma cells through certain external soluble antigens such as food proteins. These IgDs can activate basophils to secrete IL-4, IL-5, and IL-13 by interacting with Gal-9 and the CD44 complex on basophils. The secreted cytokines enhance the generation of T follicular helper type-2 cells, which secrete IL-4, and IgG1, and IgE specific for antigens recognized by the basophil-bound IgD (Shan et al., 2018). The antigen-IgD-IgDR complex on the basophil surface inhibits basophil degranulation activated by antigen-IgE-Fc ϵ RI (Shan et al., 2018). These results suggest that Gal-9 plays a role in modulating the levels of antigen-specific IgE and altering allergic inflammatory responses. The biological functions of Gal-9 are summarized in Fig. 1.

6. Galectin-10

Gal-10 or Charcot-Leyden crystal was first identified as tiny crystals in the blood and spleen of a patient who died from leukemia and was subsequently described in the sputum of patients with asthma and later as a protein closely associated with eosinophils (Su, 2018). Charcot-Leyden crystals can only be detected in humans and are thus considered a human-specific protein (Choi et al., 2017). Charcot-Leyden crystal is a naturally forming crystal with hexagonal and bipyramidal forms. It has been reported that Gal-10 binds weakly to lactose and N-acetyl-D-glucosamine (Dyer and Rosenberg, 1996; Leonidas et al., 1995; Su et al., 2018). A large amount of Gal-10 is present in human eosinophils, which accounts for 7–10% of the total proteins (Acharya and Ackerman, 2014). It is the fifth most abundant protein in eosinophils (Wilkerson et al., 2016). In addition to that in eosinophils, Gal-10 is also observed in human basophils (Calafat et al., 1997), regulatory T cells (Kubach et al., 2007), and IL-22-producing T cells (Noh et al., 2016). Gal-10 is found in the cytoplasm of eosinophils and not in the secretory granules (Ueki et al., 2018). It is crystalized and externalized by the occurrence of extracellular traps (ETosis), a suicidal cell-death process, which develops net-like chromatin (Ueki et al., 2018). These extracellular traps are composed of chromatin and granule proteins, which bind and kill extracellular pathogens (Fuchs et al., 2007).

Gal-10 are recognized as markers for eosinophilic inflammation, which can be found in secretions, tissues, and bodily fluids (Ueki et al.,

2019). Gal-10 can be used as a biomarker for assisting in the diagnosis of eosinophilic inflammation in patients with allergic asthma. Gal-10 levels in sputum are strongly correlated with the number of eosinophils, which can be used to accurately identify sputum eosinophilia in patients (Chua et al., 2012; Nyenhuis et al., 2019). Gal-10 is also significantly increased in patients with allergic diseases associated with eosinophils such as eosinophilic esophagitis (Chua et al., 2012), aspirin-induced asthma (Devouassoux et al., 2008), allergic rhinitis (Wu et al., 2018a), chronic rhinosinusitis with nasal polyps (Wu et al., 2018a, b), allergic aspergillus sinusitis (Katzenstein et al., 1983), and allergic bronchopulmonary aspergillosis (Bosken et al., 1988). Gal-10 is also increased in sera and lesional skin of patients with atopic dermatitis and is positively correlated with atopic dermatitis severity. Increased Gal-10 in atopic dermatitis is due to its elevated expression in IL-22-producing T cells but not in eosinophils, as there is no positive correlation between Gal-10 in sera and eosinophil number (Noh et al., 2016).

Amino acids Glu10, Tyr69, Lys99, and Tyr139 are important for the autocrystallization behavior of Gal-10. Recombinant Gal-10 autocrystallizes at concentrations of 2–4.5 mg/mL. The Tyr69 to Glu mutation inhibits the crystallization behavior of Gal-10, which is soluble up to 20 mg/mL in phosphate-buffered saline (Persson et al., 2019). Further, injection of Gal-10 crystals into the airways promotes Th2-cell priming by dendritic cells, which simultaneously induces airway eosinophilia (Persson et al., 2019). Airway inflammation induced by Gal-10 crystals is reduced by a crystal-dissolving monoclonal antibody against Tyr69 of Gal-10 (Persson et al., 2019). Gal-10 also activates the inflammasome pathway by inducing Nod-like receptor protein 3 and IL-1 β expression in dendritic cells (Persson et al., 2019) and macrophages (Rodríguez-Alcazar et al., 2019). Moreover, Gal-10 activates nasal epithelial cells to secrete granulocyte-macrophage colony-stimulating factor, TNF- α , and IL-1, which recruit neutrophils and enhance neutrophil activation by intensifying neutrophil extracellular traps (Gevaert et al., 2020). The biological functions of Gal-10 are summarized in Fig. 1.

7. Galectin-14

Galectin-14 was identified in sheep, which shows 58% and 57% similarity to rat and human galectin-9, respectively. It was detected in activated eosinophils. It has also been detected in eosinophils but not in neutrophils, macrophages, or lymphocytes isolated from the lungs of an ovine model of asthma induced by house dust mite, thus suggesting the role of galectin-14 in the pathological manifestations of allergic asthma (Dunphy et al., 2002).

8. Factors to consider in galectin research

Galectins are multifunctional in the regulation of allergic inflammation. They can be both positive or negative regulators of allergic inflammatory reactions, which suggest plasticity in their isoforms, cellular localization, and interacting proteins due to different stimulants. These might account in part for some contrasting reports on the functions of galectins. The biological mechanisms concerning differences in biological effects of galectins are unknown. An increase or decrease in galectin levels might be the consequence but not the cause of diseases, which further enhances the complexity in identifying the exact role of galectins. Galectin knockout, conditional knockout mice, or adoptive transfer, but not exogenously added recombinant proteins, are better methods to determine the roles of galectin in allergic inflammatory diseases. In addition, special care should be taken in interpretation of the results from studies employing inhibitors. Inhibitors can interact with other molecules or modulate non-specific pathways, which results in biased reports. This also applies to neutralizing antibodies. Information concerning the binding epitope should be included to specify whether the antibody influences the carbohydrate binding or the interaction between galectins itself (i.e. dimer or multimer formation). Antibody specificities should also be documented, as similarities exist in CBDs

between galectins.

Several studies have mentioned galectin levels in sera or various tissues, and some of them correlated these with disease severity. Altered levels of galectins return to a normal range when the disease is properly treated; therefore, several studies have suggested that the level of galectins can act as a marker for disease progression and treatment outcomes. However, it is too early to conclude on the direct association between galectins and disease pathogenesis. Samples are generally collected at the endpoint of disease or when the disease is still in progression. Altered levels of galectin in the disease state might be a side effect of the “true” damaged biological process. Otherwise, they might actively participate in disease pathogenesis or act as a regulator to compensate for altered biological functions. More detailed studies should be conducted to understand the role that galectins play in diseases.

Studies employing recombinant galectins to address the functions might also contribute to contradictory results. It is hypothesized that galectins could be transported to the extracellular space via extracellular vesicles from galectin-expressing cells or when these cells are damaged. Galectins in the extracellular space can subsequently bind to cell-surface glycoproteins via their carbohydrate binding activities to stimulate signal transduction pathways. With the concentration of galectin being higher around secreted cells, it is sensible for the galectins to bind to cell surface receptors in the local environment. However, whether they will bind to the specific cells in question or other cells or extracellular matrices in the neighborhood cannot be predicted. As for the administration of recombinant galectins animals, it is not likely those added galectins will specifically bind the specific receptors on the cells in questions through the CRD domain, as they might bind to other glycoproteins on the surface of these cells, on other cells, or glycoproteins in the body fluid.

9. Conclusion

Galectins are a group of proteins with enigmatic biochemical and biological properties. In allergic inflammatory reactions, Gal-1, 3, 9, and 10 modulate leukocyte activities by altering the levels of cytokines and chemokines. Gal-7 is generally restricted to coordinating the function of epithelial cells. Both clinical and animal data support the role of galectins in allergy pathogenesis. According to the biological functions identified for Gal-1, 3, 9, 7, and 10, allergic inflammation can be modulated by enhancing Gal-1 or inhibiting Gal-3, 7, 9, or 10. For Gal-1, overexpression by specific gene delivery systems in T cells, lung epithelial cells, or eosinophils can be employed to suppress allergic inflammation. As for inhibiting Gal-3, 9, 7, and 10, monoclonal antibodies specific for individual galectins can potentially be applied. It should be achievable to generate antibodies that do not exhibit cross reactivities to other galectins. However, a major issue to consider is whether these galectins contribute to allergic inflammation through their intracellular actions. In that case, antibodies will not be suitable and cell-permeable inhibitors will need to be employed. In addition to acting as molecular targets for the treatment of allergic diseases, some galectins may serve as potential markers for treatment outcomes. The levels of Gal-3, 9, and 10 may be downregulated when allergic inflammation is resolved.

In this review, we found that some galectins have similar biological effects on allergic inflammation. For example, except for Gal-7, Gal-1, 3, 9, and 10 are associated with the biological functions of eosinophils. It is not yet known whether there are any intracellular interactions or crosstalk between these galectins. In animal models of allergic diseases, the levels of Gal-3, 7, and 9 may be increased, and they may act additively or synergistically to enhance allergic inflammation. Galectins may influence each other's levels or biological activities. However, studies of asthma or other allergic inflammatory diseases employing genetically engineered mice with specific deletion of one galectin indicated that the effect of deleting one galectin is not compensated by the presence of

other galectins. Thus, potential crosstalk between galectins in modulating allergic inflammation requires further investigations. Further studies on the mechanisms involved in regulating galectin expression and altered signaling pathways will generate a more thorough understanding of the functions of these proteins.

Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

- Aanhane, E., Schulken, I.A., Heusschen, R., Castricum, K., Leffler, H., Griffioen, A.W., Thijssen, V.L., 2018. Different angioregulatory activity of monovalent galectin-9 isoforms. *Angiogenesis* 21 (3), 545–555.
- Acharya, K.R., Ackerman, S.J., 2014. Eosinophil granule proteins: form and function. *J. Biol. Chem.* 289 (25), 17406–17415.
- Advedissian, T., Deshayes, F., Viguié, M., 2017. Galectin-7 in epithelial homeostasis and carcinomas. *Int. J. Mol. Sci.* 18 (12).
- Al-Salam, S., Hashmi, S., 2014. Galectin-1 in early acute myocardial infarction. *PLoS One* 9 (1), e86994.
- Albrandt, K., Orida, N.K., Liu, F.T., 1987. An IgE-binding protein with a distinctive repetitive sequence and homology with an IgG receptor. *Proc. Natl. Acad. Sci. U. S. A.* 84 (19), 6859–6863.
- Baston, J.L., Baranao, R.I., Ricci, A.G., Bilotas, M.A., Olivares, C.N., Singla, J.J., Gonzalez, A.M., Stupirski, J.C., Croci, D.O., Rabinovich, G.A., Meresman, G.F., 2014. Targeting galectin-1-induced angiogenesis mitigates the severity of endometriosis. *J. Pathol.* 234 (3), 329–337.
- Blois, S.M., Ilarregui, J.M., Tometten, M., Garcia, M., Orsal, A.S., Cordo-Russo, R., Toscano, M.A., Bianco, G.A., Kobelt, P., Handjiski, B., Tirado, I., Markert, U.R., Klapp, B.F., Poirier, F., Szekeres-Bartho, J., Rabinovich, G.A., Arck, P.C., 2007. A pivotal role for galectin-1 in fetomaternal tolerance. *Nat. Med.* 13 (12), 1450–1457.
- Bosken, C.H., Myers, J.L., Greenberger, P.A., Katzenstein, A.L., 1988. Pathologic features of allergic bronchopulmonary aspergillosis. *Am. J. Surg. Pathol.* 12 (3), 216–222.
- Bourdonnay, E., Zaslona, Z., Penke, L.R., Speth, J.M., Schneider, D.J., Przybranowski, S., Swanson, J.A., Mancuso, P., Freeman, C.M., Curtis, J.L., Peters-Golden, M., 2015. Transcellular delivery of vesicular SOCS proteins from macrophages to epithelial cells blunts inflammatory signaling. *J. Exp. Med.* 212 (5), 729–742.
- Brewer, C.F., 2002. Thermodynamic binding studies of galectin-1, -3 and -7. *Glycoconj. J.* 19 (7–9), 459–465.
- Burks, A.W., Tang, M., Sicherer, S., Muraro, A., Eigenmann, P.A., Ebisawa, M., Fiocchi, A., Chiang, W., Beyer, K., Wood, R., Hourihane, J., Jones, S.M., Lack, G., Sampson, H.A., 2012. ICON: food allergy. *J. Allergy Clin. Immunol.* 129 (4), 906–920.
- Calafat, J., Janssen, H., Knol, E.F., Weller, P.F., Egesten, A., 1997. Ultrastructural localization of Charcot-Leyden crystal protein in human eosinophils and basophils. *Eur. J. Haematol.* 58 (1), 56–66.
- Casals, C., Campanero-Rhodes, M.A., Garcia-Fojeda, B., Solis, D., 2018. The role of collectins and galectins in lung innate immune defense. *Front. Immunol.* 9, 1998.
- Cerra, R.F., Gitt, M.A., Barondes, S.H., 1985. Three soluble rat beta-galactoside-binding lectins. *J. Biol. Chem.* 260 (19), 10474–10477.
- Chen, H.Y., Sharma, B.B., Yu, L., Zuberi, R., Weng, I.C., Kawakami, Y., Kawakami, T., Hsu, D.K., Liu, F.T., 2006. Role of galectin-3 in mast cell functions: galectin-3-deficient mast cells exhibit impaired mediator release and defective JNK expression. *J. Immunol.* 177 (8), 4991–4997.
- Chen, X., Song, C.H., Liu, Z.Q., Feng, B.S., Zheng, P.Y., Li, P., In, S.H., Tang, S.G., Yang, P.C., 2011. Intestinal epithelial cells express galectin-9 in patients with food allergy that plays a critical role in sustaining allergic status in mouse intestine. *Allergy* 66 (8), 1038–1046.

- Choi, E., Miller, A.D., Devenish, E., Asakawa, M., McConkey, M., Peters-Kennedy, J., 2017. Charcot-Leyden crystals: do they exist in veterinary species? A case report and literature review. *J. Vet. Diagn. Invest.* 29 (6), 904–909.
- Chua, J.C., Douglass, J.A., Gillman, A., O'Hehir, R.E., Meeseus, E.N., 2012. Galectin-10, a potential biomarker of eosinophilic airway inflammation. *PLoS One* 7 (8), e42549.
- Coca, A.F., Cooke, R.A., 1923. On the classification of the phenomena of hypersensitivity. *J. Immunol.* 8 (3), 163–182.
- Dalotto-Moreno, T., Croci, D.O., Cerliani, J.P., Martinez-Allo, V.C., Dergan-Dylon, S., Mendez-Huergo, S.P., Stupirski, J.C., Mazal, D., Osinaga, E., Toscano, M.A., Sundblad, V., Rabinovich, G.A., Salatino, M., 2013. Targeting galectin-1 overcomes breast cancer-associated immunosuppression and prevents metastatic disease. *Canc. Res.* 73 (3), 1107–1117.
- Davicino, R.C., Mendez-Huergo, S.P., Elicabe, R.J., Stupirski, J.C., Autenrieth, I., Di Genaro, M.S., Rabinovich, G.A., 2017. Galectin-1-Driven tolerogenic programs aggravate *Yersinia enterocolitica* infection by repressing antibacterial immunity. *J. Immunol.* 199 (4), 1382–1392.
- de Kivit, S., Saeland, E., Kraneveld, A.D., van de Kant, H.J., Schouten, B., van Esch, B.C., Knol, J., Sprickelman, A.B., van der Aa, L.B., Knippels, L.M., Garssen, J., van Kooijk, Y., Willemsen, L.E., 2012. Galectin-9 induced by dietary synbiotics is involved in suppression of allergic symptoms in mice and humans. *Allergy* 67 (3), 343–352.
- del Pozo, V., Rojo, M., Rubio, M.L., Cortegano, I., Cardaba, B., Gallardo, S., Ortega, M., Civantos, E., Lopez, E., Martin-Mosquero, C., Peces-Barba, G., Palomino, P., Gonzalez-Mangado, N., Lahoz, C., 2002. 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.* 166 (5), 732–737.
- Delbrouck, C., Doyen, I., Belot, N., Decaestecker, C., Ghanooni, R., de Lavareille, A., Kaltner, H., Choufani, G., Danguy, A., Vandenhoven, G., Gabius, H.J., Hassid, S., Kiss, R., 2002. Galectin-1 is overexpressed in nasal polyps under budesonide and inhibits eosinophil migration. *Lab. Invest.* 82 (2), 147–158.
- Detting, L., Rubinstein, N., Aoki, A., Rabinovich, G.A., Maldonado, C.A., 2003. Regulated expression and ultrastructural localization of galectin-1, a proapoptotic beta-galactoside-binding lectin, during spermatogenesis in rat testis. *Biol. Reprod.* 68 (1), 51–59.
- Devouassoux, G., Pachot, A., Laforest, L., Diasparra, J., Freymond, N., Van Ganse, E., Mouglin, B., Pacheco, Y., 2008. Galectin-10 mRNA is overexpressed in peripheral blood of aspirin-induced asthma. *Allergy* 63 (1), 125–131.
- Draijer, C., Robbe, P., Boersma, C.E., Hylkema, M.N., Melgert, B.N., 2018. Dual role of YM1+ M2 macrophages in allergic lung inflammation. *Sci. Rep.* 8 (1), 5105.
- Dunphy, J.L., Barcham, G.J., Bischof, R.J., Young, A.R., Nash, A., Meeseus, E.N., 2002. Isolation and characterization of a novel eosinophil-specific galectin released into the lungs in response to allergen challenge. *J. Biol. Chem.* 277 (17), 14916–14924.
- Dyer, K.D., Rosenberg, H.F., 1996. Eosinophil Charcot-Leyden crystal protein binds to beta-galactoside sugars. *Life Sci.* 58 (23), 2073–2082.
- Eller, E., Kjaer, H.F., Host, A., Andersen, K.E., Bindslev-Jensen, C., 2010. Development of atopic dermatitis in the DARC birth cohort. *Pediatr. Allergy Immunol.* 21 (2 Pt 1), 307–314.
- Farag, A.G.A., Al-Sharaky, D.R., Allam, S.S., Khaled, H.N., 2020. Role of galectin-9 in atopic dermatitis - is it mediated through E selectin? A clinical and immunohistochemical study. *Clin. Cosmet. Invest. Dermatol.* 13, 11–19.
- Forsman, H., Islander, U., Andreasson, E., Andersson, A., Onnheim, K., Karlstrom, A., Savman, K., Magnusson, M., Brown, K.L., Karlsson, A., 2011. Galectin 3 aggravates joint inflammation and destruction in antigen-induced arthritis. *Arthritis Rheum.* 63 (2), 445–454.
- Fuchs, T.A., Abed, U., Goosmann, C., Hurwitz, R., Schulze, I., Wahn, V., Weinrauch, Y., Brinkmann, V., Zychlinsky, A., 2007. Novel cell death program leads to neutrophil extracellular traps. *J. Cell Biol.* 176 (2), 231–241.
- Fuertes, M.B., Molinero, L.L., Toscano, M.A., Ilarregui, J.M., Rubinstein, N., Fainboim, L., Zwierner, N.W., Rabinovich, G.A., 2004. Regulated expression of galectin-1 during T-cell activation involves Lck and Fyn kinases and signaling through MEK1/ERK, p38 MAP kinase and p70S6 kinase. *Mol. Cell. Biochem.* 267 (1–2), 177–185.
- Fukushima, A., Sumi, T., Fukuda, K., Kumagai, N., Nishida, T., Okumura, K., Akiba, H., Yagita, H., Ueno, H., 2008. Roles of galectin-9 in the development of experimental allergic conjunctivitis in mice. *Int. Arch. Allergy Immunol.* 146 (1), 36–43.
- Garin, M.I., Chu, C.C., Golshayan, D., Cernuda-Morollon, E., Wait, R., Lechler, R.I., 2007. Galectin-1: a key effector of regulation mediated by CD4+CD25+ T cells. *Blood* 109 (5), 2058–2065.
- Ge, X.N., Bahaie, N.S., Kang, B.N., Hosseinkhani, M.R., Ha, S.G., Frenzel, E.M., Liu, F.T., Rao, S.P., Sriramarao, P., 2010. Allergen-induced airway remodeling is impaired in galectin-3-deficient mice. *J. Immunol.* 185 (2), 1205–1214.
- Ge, X.N., Ha, S.G., Liu, F.T., Rao, S.P., Sriramarao, P., 2013. Eosinophil-expressed galectin-3 regulates cell trafficking and migration. *Front. Pharmacol.* 4, 37.
- Ge, X.N., Ha, S.G., Greenberg, Y.G., Rao, A., Bastan, I., Blidner, A.G., Rao, S.P., Rabinovich, G.A., Sriramarao, P., 2016. Regulation of eosinophilia and allergic airway inflammation by the glycan-binding protein galectin-1. *Proc. Natl. Acad. Sci. U. S. A.* 113 (33), E4837–E4846.
- Gevaert, E., Delemarre, T., De Volder, J., Zhang, N., Holtappels, G., De Ruyck, N., Persson, E., Heyndrickx, I., Verstraete, K., Aegerter, H., Nauwynck, H., Savvides, S. N., Lambrecht, B.N., Bachert, C., 2020. Charcot-Leyden crystals promote neutrophilic inflammation in patients with nasal polyposis. *J. Allergy Clin. Immunol.* 145 (1), 427–430 e424.
- Han, H., Roan, F., Ziegler, S.F., 2017. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol. Rev.* 278 (1), 116–130.
- Heusschen, R., Schulkens, I.A., van Beijnum, J., Griffioen, A.W., Thijssen, V.L., 2014. Endothelial LGALS9 splice variant expression in endothelial cell biology and angiogenesis. *Biochim. Biophys. Acta* 1842 (2), 284–292.
- Hirashima, M., 2000. Ecalectin/galectin-9, a novel eosinophil chemoattractant: its function and production. *Int. Arch. Allergy Immunol.* 122 (Suppl. 1), 6–9.
- Ho, M.K., Springer, T.A., 1982. Mac-2, a novel 32,000 Mr mouse macrophage subpopulation-specific antigen defined by monoclonal antibodies. *J. Immunol.* 128 (3), 1221–1228.
- Horlacher, T., Oberli, M.A., Werz, D.B., Krock, L., Bufali, S., Mishra, R., Sobek, J., Simons, K., Hirashima, M., Niki, T., Seeberger, P.H., 2010. Determination of carbohydrate-binding preferences of human galectins with carbohydrate microarrays. *ChemBiochem* 11 (11), 1563–1573.
- Hsu, D.K., Yang, R.Y., Pan, Z., Yu, L., Salomon, D.R., Fung-Leung, W.P., Liu, F.T., 2000. Targeted disruption of the galectin-3 gene results in attenuated peritoneal inflammatory responses. *Am. J. Pathol.* 156 (3), 1073–1083.
- Hsu, D.K., Chernyavsky, A.I., Chen, H.Y., Yu, L., Grando, S.A., Liu, F.T., 2009. Endogenous galectin-3 is localized in membrane lipid rafts and regulates migration of dendritic cells. *J. Invest. Dermatol.* 129 (3), 573–583.
- Ilarregui, J.M., Croci, D.O., Bianco, G.A., Toscano, M.A., Salatino, M., Vermeulen, M.E., Geffner, J.R., Rabinovich, G.A., 2009. Tolerogenic signals delivered by dendritic cells to T cells through a galectin-1-driven immunoregulatory circuit involving interleukin 27 and interleukin 10. *Nat. Immunol.* 10 (9), 981–991.
- John, S., Mishra, R., 2016. Galectin-9: from cell biology to complex disease dynamics. *J. Biosci.* 41 (3), 507–534.
- Jones, C., Mackay, A., Grigoriadis, A., Cossu, A., Reis-Filho, J.S., Fulford, L., Dexter, T., Davies, S., Bulmer, K., Ford, E., Parry, S., Budroni, M., Palmieri, G., Neville, A.M., O'Hare, M.J., Lakhani, S.R., 2004. Expression profiling of purified normal human luminal and myoepithelial breast cells: identification of novel prognostic markers for breast cancer. *Canc. Res.* 64 (9), 3037–3045.
- Katzenstein, A.L., Sale, S.R., Greenberger, P.A., 1983. Allergic Aspergillus sinusitis: a newly recognized form of sinusitis. *J. Allergy Clin. Immunol.* 72 (1), 89–93.
- Kay, J., Gawkrödger, D.J., Mortimer, M.J., Jaron, A.G., 1994. The prevalence of childhood atopic eczema in a general population. *J. Am. Acad. Dermatol.* 30 (1), 35–39.
- Kimata, H., 2002. Enhancement of IgE production in B cells by neutrophils via galectin-3 in IgE-associated atopic eczema/dermatitis syndrome. *Int. Arch. Allergy Immunol.* 128 (2), 168–170.
- Kimata, H., 2007. Specific allergen enhances IgE production via galectin-3 in surface IgE + B cells. *Eur. J. Clin. Invest.* 37 (12), 1001–1002.
- Kubach, J., Lutter, P., Bopp, T., Stoll, S., Becker, C., Huter, E., Richter, C., Weingarten, P., Warger, T., Knop, J., Mullner, S., Wijdenes, J., Schild, H., Schmitt, E., Jonuleit, H., 2007. Human CD4+CD25+ regulatory T cells: proteome analysis identifies galectin-10 as a novel marker essential for their energy and suppressive function. *Blood* 110 (5), 1550–1558.
- Lack, G., Fox, D., Northstone, K., Golding, J., Avon longitudinal study of, P., Children Study, T., 2003. Factors associated with the development of peanut allergy in childhood. *N. Engl. J. Med.* 348 (11), 977–985.
- Leal-Pinto, E., Tao, W., Rappaport, J., Richardson, M., Knorr, B.A., Abramson, R.G., 1997. Molecular cloning and functional reconstitution of a urate transporter/channel. *J. Biol. Chem.* 272 (1), 617–625.
- Leonidas, D.D., Elbert, B.L., Zhou, Z., Leffler, H., Ackerman, S.J., Acharya, K.R., 1995. Crystal structure of human Charcot-Leyden crystal protein, an eosinophil lysophospholipase, identifies it as a new member of the carbohydrate-binding family of galectins. *Structure* 3 (12), 1379–1393.
- Li, M.L., Su, X.M., Ren, Y., Zhao, X., Kong, L.F., Kang, J., 2020. HDAC8 inhibitor attenuates airway responses to antigen stimulus through synchronously suppressing galectin-3 expression and reducing macrophage-2 polarization. *Respir. Res.* 21 (1), 62.
- Liu, F.T., 2000. Galectins: a new family of regulators of inflammation. *Clin. Immunol.* 97 (2), 79–88.
- Liu, F.T., 2005. Regulatory roles of galectins in the immune response. *Int. Arch. Allergy Immunol.* 136 (4), 385–400.
- Liu, F.T., Rabinovich, G.A., 2010. Galectins: regulators of acute and chronic inflammation. *Ann. N. Y. Acad. Sci.* 1183, 158–182.
- Lopez, E., del Pozo, V., Miguel, T., Sastre, B., Seoane, C., Civantos, E., Llanes, E., Baeza, M.L., Palomino, P., Cardaba, B., Gallardo, S., Manzarbeitia, F., Zubeldia, J.M., Lahoz, C., 2006. Inhibition of chronic airway inflammation and remodeling by galectin-3 gene therapy in a murine model. *J. Immunol.* 176 (3), 1943–1950.
- Lopez, E., Zafra, M.P., Sastre, B., Gamez, C., Lahoz, C., del Pozo, V., 2011. Gene expression profiling in lungs of chronic asthmatic mice treated with galectin-3: downregulation of inflammatory and regulatory genes. *Mediat. Inflamm.* 2011, 823279.
- Lotan, R., Carralero, D., Lotan, D., Raz, A., 1989. Biochemical and immunological characterization of K-1735P melanoma galactoside-binding lectins and their modulation by differentiation inducers. *Canc. Res.* 49 (5), 1261–1268.
- Madsen, P., Rasmussen, H.H., Flint, T., Gromov, P., Kruse, T.A., Honore, B., Vorum, H., Celis, J.E., 1995. Cloning, expression, and chromosome mapping of human galectin-7. *J. Biol. Chem.* 270 (11), 5823–5829.
- Magnaldo, T., Berner, F., Darmon, M., 1995. Galectin-7, a human 14-kDa S-lectin, specifically expressed in keratinocytes and sensitive to retinoic acid. *Dev. Biol.* 168 (2), 259–271.
- Magnaldo, T., Fowles, D., Darmon, M., 1998. Galectin-7, a marker of all types of stratified epithelia. *Differentiation* 63 (3), 159–168.
- Martinez-Bosch, N., Navarro, P., 2020. Galectins in the tumor microenvironment: focus on galectin-1. *Adv. Exp. Med. Biol.* 1259, 17–38.
- Matsumoto, R., Matsumoto, H., Seki, M., Hata, M., Asano, Y., Kanegasaki, S., Stevens, R. L., Hirashima, M., 1998. Human ecalectin, a variant of human galectin-9, is a novel eosinophil chemoattractant produced by T lymphocytes. *J. Biol. Chem.* 273 (27), 16976–16984.

- Mizuno, M., Sakaguchi, K., Sakane, I., 2020. Oral administration of fucoidan can exert anti-allergic activity after allergen sensitization by enhancement of galectin-9 secretion in blood. *Biomolecules* 10 (2).
- Moreira, A.P., Cavassani, K.A., Hullinger, R., Rosada, R.S., Fong, D.J., Murray, L., Hesson, D.P., Hogaboam, C.M., 2010. Serum amyloid P attenuates M2 macrophage activation and protects against fungal spore-induced allergic airway disease. *J. Allergy Clin. Immunol.* 126 (4), 712–721 e717.
- Nakajima, R., Miyagaki, T., Oka, T., Nakao, M., Kawaguchi, M., Suga, H., Morimura, S., Kai, H., Asano, Y., Tada, Y., Kadono, T., Sato, S., Sugaya, M., 2015. Elevated serum galectin-9 levels in patients with atopic dermatitis. *J. Dermatol.* 42 (7), 723–726.
- Niiyama, S., Yoshino, T., Yasuda, C., Yu, X., Izumi, R., Ishiwatari, S., Matsukuma, S., Mukai, H., 2016. Galectin-7 in the stratum corneum: a biomarker of the skin barrier function. *Int. J. Cosmet. Sci.* 38 (5), 487–495.
- Nio-Kobayashi, J., 2017. Tissue- and cell-specific localization of galectins, beta-galactose-binding animal lectins, and their potential functions in health and disease. *Anat. Sci. Int.* 92 (1), 25–36.
- Nofal, E., Eldesoky, F., Nofal, A., Abdelshafy, A., Zedan, A., 2019. Serum galectin-9 levels in atopic dermatitis, psoriasis and allergic contact dermatitis: a cross-sectional study. *Indian J. Dermatol. Venereol. Leprol.* 85 (2), 195–196.
- Noh, S., Jin, S., Park, C.O., Lee, Y.S., Lee, N., Lee, J., Shin, J.U., Kim, S.H., Yun, K.N., Kim, J.Y., Lee, K.H., 2016. Elevated galectin-10 expression of IL-22-producing T cells in patients with atopic dermatitis. *J. Invest. Dermatol.* 136 (1), 328–331.
- Nyenhuis, S.M., Alumkal, P., Du, J., Maybruck, B.T., Vinicky, M., Ackerman, S.J., 2019. Charcot-Leyden crystal protein/galectin-10 is a surrogate biomarker of eosinophilic airway inflammation in asthma. *Biomarkers Med.* 13 (9), 715–724.
- Perez, C.V., Gomez, L.G., Gualdoni, G.S., Lustig, L., Rabinovich, G.A., Guazzone, V.A., 2015. Dual roles of endogenous and exogenous galectin-1 in the control of testicular immunopathology. *Sci. Rep.* 5, 12259.
- Persson, E.K., Verstraete, K., Heyndrickx, I., Gevaert, E., Aegerter, H., Percier, J.M., Deswarte, K., Verschueren, K.H.G., Dansercoer, A., Gras, D., Chanez, P., Bachert, C., Goncalves, A., Van Gorp, H., De Haard, H., Blanchetot, C., Saunders, M., Hammad, H., Savvides, S.N., Lambrecht, B.N., 2019. Protein crystallization promotes type 2 immunity and is reversible by antibody treatment. *Science* 364 (6442).
- Poncin, C.V., Illarregui, J.M., Battalla, E.I., Engels, S., Cerliani, J.P., Cucher, M.A., van Kooyk, Y., Gonzalez-Cappa, S.M., Rabinovich, G.A., 2015. Trypanosoma cruzi infection imparts a regulatory program in dendritic cells and T cells via galectin-1-dependent mechanisms. *J. Immunol.* 195 (7), 3311–3324.
- Rabinovich, G., Castagna, L., Landa, C., Riera, C.M., Sotomayor, C., 1996. Regulated expression of a 16-kd galectin-like protein in activated rat macrophages. *J. Leukoc. Biol.* 59 (3), 363–370.
- Ramhorst, R.E., Giribaldi, L., Fraccaroli, L., Toscano, M.A., Stupirski, J.C., Romero, M.D., Durand, E.S., Rubinstein, N., Blaschitz, A., Sedlmayr, P., Genti-Raimondi, S., Fainboim, L., Rabinovich, G.A., 2012. Galectin-1 confers immune privilege to human trophoblast: implications in recurrent fetal loss. *Glycobiology* 22 (10), 1374–1386.
- Rance, F., 2008. Food allergy in children suffering from atopic eczema. *Pediatr. Allergy Immunol.* 19 (3), 279–284 quiz 285.
- Rao, S.P., Wang, Z., Zuberi, R.I., Sikora, L., Bahaie, N.S., Zuraw, B.L., Liu, F.T., Sriramara, P., 2007. Galectin-3 functions as an adhesion molecule to support eosinophil rolling and adhesion under conditions of flow. *J. Immunol.* 179 (11), 7800–7807.
- Rao, S.P., Ge, X.N., Sriramara, P., 2017. Regulation of eosinophil recruitment and activation by galectins in allergic asthma. *Front. Med.* 4, 68.
- Rhodes, H.L., Sporik, R., Thomas, P., Holgate, S.T., Cogswell, J.J., 2001. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. *J. Allergy Clin. Immunol.* 108 (5), 720–725.
- Rhodes, H.L., Thomas, P., Sporik, R., Holgate, S.T., Cogswell, J.J., 2002. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am. J. Respir. Crit. Care Med.* 165 (2), 176–180.
- Ridano, M.E., Subirada, P.V., Paz, M.C., Lorenc, V.E., Stupirski, J.C., Gramajo, A.L., Luna, J.D., Croci, D.O., Rabinovich, G.A., Sanchez, M.C., 2017. Galectin-1 expression imprints a neurovascular phenotype in proliferative retinopathies and delineates responses to anti-VEGF. *Oncotarget* 8 (20), 32505–32522.
- Robbe, P., Draijer, C., Borg, T.R., Luinge, M., Timens, W., Wouters, I.M., Melgert, B.N., Hylkema, M.N., 2015. Distinct macrophage phenotypes in allergic and nonallergic lung inflammation. *Am. J. Physiol. Lung Cell Mol. Physiol.* 308 (4), L358–L367.
- Robertson, M.W., Liu, F.T., 1991. Heterogeneous IgE glycoforms characterized by differential recognition of an endogenous lectin (IgE-binding protein). *J. Immunol.* 147 (9), 3024–3030.
- Rodriguez-Alcázar, J.F., Ataide, M.A., Engels, G., Schmitt-Mabumnyo, C., Garbi, N., Kastenmuller, W., Latz, E., Franklin, B.S., 2019. Charcot-leyden crystals activate the NLRP3 inflammasome and cause IL-1 β inflammation in human macrophages. *J. Immunol.* 202 (2), 550–558.
- Roff, C.F., Wang, J.L., 1983. Endogenous lectins from cultured cells. Isolation and characterization of carbohydrate-binding proteins from 3T3 fibroblasts. *J. Biol. Chem.* 258 (17), 10657–10663.
- Saegusa, J., Hsu, D.K., Chen, H.Y., Yu, L., Fermin, A., Fung, M.A., Liu, F.T., 2009. Galectin-3 is critical for the development of the allergic inflammatory response in a mouse model of atopic dermatitis. *Am. J. Pathol.* 174 (3), 922–931.
- Sanchez-Cuellar, S., de la Fuente, H., Cruz-Adalia, A., Lamana, A., Cibrian, D., Giron, R. M., Vara, A., Sanchez-Madrid, F., Ancochea, J., 2012. Reduced expression of galectin-1 and galectin-9 by leucocytes in asthma patients. *Clin. Exp. Immunol.* 170 (3), 365–374.
- Sano, H., Hsu, D.K., Apgar, J.R., Yu, L., Sharma, B.B., Kuwabara, I., Izui, S., Liu, F.T., 2003. Critical role of galectin-3 in phagocytosis by macrophages. *J. Clin. Invest.* 112 (3), 389–397.
- Santucci, L., Fiorucci, S., Rubinstein, N., Mencarelli, A., Palazzetti, B., Federici, B., Rabinovich, G.A., Morelli, A., 2003. Galectin-1 suppresses experimental colitis in mice. *Gastroenterology* 124 (5), 1381–1394.
- Sato, S., Hughes, R.C., 1992. Binding specificity of a baby hamster kidney lectin for H type I and II chains, polylectosamine glycans, and appropriately glycosylated forms of laminin and fibronectin. *J. Biol. Chem.* 267 (10), 6983–6990.
- Sato, M., Nishi, N., Shoji, H., Seki, M., Hashidate, T., Hirabayashi, J., Kasai, K., Hata, Y., Suzuki, S., Hirashima, M., Nakamura, T., 2002. Functional analysis of the carbohydrate recognition domains and a linker peptide of galectin-9 as to eosinophil chemottractant activity. *Glycobiology* 12 (3), 191–197.
- Seropian, I.M., Cerliani, J.P., Toldo, S., Van Tassell, B.W., Illarregui, J.M., Gonzalez, G.E., Matoso, M., Salloum, F.N., Melchior, R., Gelpi, R.J., Stupirski, J.C., Benatar, A., Gomez, K.A., Morales, C., Abbate, A., Rabinovich, G.A., 2013. Galectin-1 controls cardiac inflammation and ventricular remodeling during acute myocardial infarction. *Am. J. Pathol.* 182 (1), 29–40.
- Shan, M., Carrillo, J., Yeste, A., Gutzeit, C., Segura-Garzon, D., Walland, A.C., Pybus, M., Grasset, E.K., Yeiser, J.R., Matthews, D.B., van de Veen, W., Comerma, L., He, B., Boonpiyathad, T., Lee, H., Blanco, J., Osborne, L.C., Siracusa, M.C., Akdis, M., Artis, D., Mehandru, S., Sampson, H.A., Berin, M.C., Chen, K., Cerutti, A., 2018. Secreted IgD amplifies humoral T helper 2 cell responses by binding basophils via galectin-9 and CD44. *Immunity* 49 (4), 709–724 e708.
- Sicherer, S.H., Leung, D.Y., 2014. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2013. *J. Allergy Clin. Immunol.* 133 (2), 324–334.
- Starosom, S.C., Mascanfroni, I.D., Imitola, J., Cao, L., Raddassi, K., Hernandez, S.F., Bassil, R., Croci, D.O., Cerliani, J.P., Delacour, D., Wang, Y., Elyaman, W., Khoury, S. J., Rabinovich, G.A., 2012. Galectin-1 deactivates classically activated microglia and protects from inflammation-induced neurodegeneration. *Immunity* 37 (2), 249–263.
- Stowell, S.R., Qian, Y., Karmakar, S., Koyama, N.S., Dias-Baruffi, M., Leffler, H., McEver, R.P., Cummings, R.D., 2008. Differential roles of galectin-1 and galectin-3 in regulating leukocyte viability and cytokine secretion. *J. Immunol.* 180 (5), 3091–3102.
- Stowell, S.R., Cho, M., Feasley, C.L., Arthur, C.M., Song, X., Colucci, J.K., Karmakar, S., Mehta, P., Dias-Baruffi, M., McEver, R.P., Cummings, R.D., 2009. Ligand reduces galectin-1 sensitivity to oxidative inactivation by enhancing dimer formation. *J. Biol. Chem.* 284 (8), 4989–4999.
- Su, J., 2018. A brief history of charcot-leyden crystal protein/galectin-10 research. *Molecules* 23 (11).
- Su, J., Gao, J., Si, Y., Cui, L., Song, C., Wang, Y., Wu, R., Tai, G., Zhou, Y., 2018. Galectin-10: a new structural type of prototype galectin dimer and effects on saccharide ligand binding. *Glycobiology* 28 (3), 159–168.
- Sundblad, V., Moros, L.G., Geffner, J.R., Rabinovich, G.A., 2017. Galectin-1: a jack-of-all-trades in the resolution of acute and chronic inflammation. *J. Immunol.* 199 (11), 3721–3730.
- Suryawanshi, A., Cao, Z., Thitprasert, T., Zaidi, T.S., Panjwani, N., 2013. Galectin-1-mediated suppression of Pseudomonas aeruginosa-induced corneal immunopathology. *J. Immunol.* 190 (12), 6397–6409.
- Sziksz, E., Kozma, G.T., Pallinger, E., Komlosi, Z.I., Adori, C., Kovacs, L., Szebeni, B., Rusai, K., Losonczy, G., Szabo, A., Vannay, A., 2010. Galectin-9 in allergic airway inflammation and hyper-responsiveness in mice. *Int. Arch. Allergy Immunol.* 151 (4), 308–317.
- Tanino, Y., Hashimoto, T., Ojima, T., Mizuno, M., 2016. F-fucoidan from Saccharina japonica is a novel inducer of galectin-9 and exhibits anti-allergic activity. *J. Clin. Biochem. Nutr.* 59 (1), 25–30.
- Tesone, A.J., Rutkowski, M.R., Brencicova, E., Svoronos, N., Perales-Puchalt, A., Stephen, T.L., Allegranza, M.J., Payne, K.K., Nguyen, J.M., Wickramasinghe, J., Tchou, J., Borowsky, M.E., Rabinovich, G.A., Kossenkov, A.V., Conejo-Garcia, J.R., 2016. Satb1 overexpression drives tumor-promoting activities in cancer-associated dendritic cells. *Cell Rep.* 14 (7), 1774–1786.
- Tian, J., He, R., Fan, Y., Zhang, Q., Tian, B., Zhou, C., Liu, C., Song, M., Zhao, S., 2020. Galectin-7 overexpression destroys airway epithelial barrier in transgenic mice. *Integr. Zool.* <https://doi.org/10.1111/1749-4877.12463>.
- Truong, M.J., Gruart, V., Kusnier, J.P., Papin, J.P., Loiseau, S., Capron, A., Capron, M., 1993. Human neutrophils express immunoglobulin E (IgE)-binding proteins (Mac-2/epsilon BP) of the S-type lectin family: role in IgE-dependent activation. *J. Exp. Med.* 177 (1), 243–248.
- Tsakok, T., Marrs, T., Mohsin, M., Baron, S., du Toit, G., Till, S., Flohr, C., 2016. Does atopic dermatitis cause food allergy? A systematic review. *J. Allergy Clin. Immunol.* 137 (4), 1071–1078.
- Tureci, O., Schmitt, H., Fadle, N., Pfreundschuh, M., Sahin, U., 1997. Molecular definition of a novel human galectin which is immunogenic in patients with Hodgkin's disease. *J. Biol. Chem.* 272 (10), 6416–6422.
- Ueki, S., Tokunaga, T., Melo, R.C.N., Saito, H., Honda, K., Fukuchi, M., Konno, Y., Takeda, M., Yamamoto, Y., Hirokawa, M., Fujieda, S., Spencer, L.A., Weller, P.F., 2018. Charcot-Leyden crystal formation is closely associated with eosinophil extracellular trap cell death. *Blood* 132 (20), 2183–2187.
- Ueki, S., Miyabe, Y., Yamamoto, Y., Fukuchi, M., Hirokawa, M., Spencer, L.A., Weller, P. F., 2019. Charcot-leyden crystals in eosinophilic inflammation: active cytolysis leads to crystal formation. *Curr. Allergy Asthma Rep.* 19 (8), 35.
- Umayahara, T., Shimauchi, T., Iwasaki, M., Sakabe, J.I., Aoshima, M., Nakazawa, S., Yatagai, T., Yamaguchi, H., Phadungsakawadi, P., Kurihara, K., Tokura, Y., 2020. Protective role of Galectin-7 for skin barrier impairment in atopic dermatitis. *Clin. Exp. Allergy* 50 (8), 922–931.
- van der Leij, J., van den Berg, A., Harms, G., Eschbach, H., Vos, H., Zwieters, P., van Weeghel, R., Groen, H., Poppema, S., Visser, L., 2007. Strongly enhanced IL-10 production using stable galectin-1 homodimers. *Mol. Immunol.* 44 (4), 506–513.

- van Esch, B., Abbring, S., Diks, M.A.P., Dingjan, G.M., Harthoorn, L.F., Vos, A.P., Garssen, J., 2016. Post-sensitization administration of non-digestible oligosaccharides and Bifidobacterium breve M-16V reduces allergic symptoms in mice. *Immun. Inflamm. Dis.* 4 (2), 155–165.
- Vergetaki, A., Jeschke, U., Vrekoussis, T., Taliouri, E., Sabatini, L., Papakonstanti, E.A., Makrigiannakis, A., 2014. Galectin-1 overexpression in endometriosis and its regulation by neuropeptides (CRH, UCN) indicating its important role in reproduction and inflammation. *PLoS One* 9 (12), e114229.
- von Kobyletzki, L.B., Bornehag, C.G., Hasselgren, M., Larsson, M., Lindstrom, C.B., Svensson, A., 2012. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. *BMC Dermatol.* 12, 11.
- Wahn, U., 2000. What drives the allergic march? *Allergy* 55 (7), 591–599.
- Wan, L., Liu, F.T., 2016. Galectin-3 and inflammation. *Glycobiol. Insights* 6, 1–9.
- Wilkerson, E.M., Johansson, M.W., Hebert, A.S., Westphall, M.S., Mathur, S.K., Jarjour, N.N., Schwantes, E.A., Mosher, D.F., Coon, J.J., 2016. The peripheral blood eosinophil proteome. *J. Proteome Res.* 15 (5), 1524–1533.
- Wu, D., Mueller, S.K., Nocera, A.L., Finn, K., Libermann, T.A., Bleier, B.S., 2018a. Axonal guidance signaling pathway is suppressed in human nasal polyps. *Am. J. Rhinol. Allergy* 32 (4), 208–216.
- Wu, D., Mueller, S.K., Nocera, A.L., Finn, K., Libermann, T.A., Bleier, B.S., 2018b. TREM-1 neutrophil activation pathway is suppressed in eosinophilic nasal polyps. *Am. J. Rhinol. Allergy* 32 (5), 359–368.
- Yamamoto, H., Kashio, Y., Shoji, H., Shinonaga, R., Yoshimura, T., Nishi, N., Nabe, T., Nakamura, T., Kohno, S., Hirashima, M., 2007. Involvement of galectin-9 in Guinea pig allergic airway inflammation. *Int. Arch. Allergy Immunol.* 143 (Suppl. 1), 95–105.
- Yang, R.Y., Liu, F.T., 2003. Galectins in cell growth and apoptosis. *Cell. Mol. Life Sci.* 60 (2), 267–276.
- Zaslona, Z., Przybranowski, S., Wilke, C., van Rooijen, N., Teitz-Tennenbaum, S., Osterholzer, J.J., Wilkinson, J.E., Moore, B.B., Peters-Golden, M., 2014. Resident alveolar macrophages suppress, whereas recruited monocytes promote, allergic lung inflammation in murine models of asthma. *J. Immunol.* 193 (8), 4245–4253.
- Zuberi, R.I., Hsu, D.K., Kalayci, O., Chen, H.Y., Sheldon, H.K., Yu, L., Apgar, J.R., Kawakami, T., Lilly, C.M., Liu, F.T., 2004. Critical role for galectin-3 in airway inflammation and bronchial hyperresponsiveness in a murine model of asthma. *Am. J. Pathol.* 165 (6), 2045–2053.
- Zuniga, E., Rabinovich, G.A., Iglesias, M.M., Gruppi, A., 2001. Regulated expression of galectin-1 during B-cell activation and implications for T-cell apoptosis. *J. Leukoc. Biol.* 70 (1), 73–79.