Review Article

N. Rubinstein
J.M. Ilarregui
M.A. Toscano
G.A. Rabinovich

The role of galectins in the initiation, amplification and resolution of the inflammatory response

Key words:
apoptosis; autoimmunity; cancer; galectin; galectin-1; glycoconjugates; immunosuppression; inflammation; tumour-immune escape

Acknowledgments:
Our work was supported by grants to G.A.R. from Fundación Antorchas (early career grant), Wellcome Trust International (IRDA), Ministry of Health (Beca Carrillo-Oñativia, Argentina) and a program from Fundación Sales.

G.A.R. is an associate researcher from CONICET; N.R. and M.A.T. thank CONICET for the fellowships granted; J.M.I. thanks the Argentinian Ministry of Health for the fellowship 'Carrillo-Oñativia'.

Abstract: Inflammation involves the sequential activation of signalling pathways leading to the production of both pro-inflammatory and anti-inflammatory mediators. Galectins constitute a family of structurally related β-galactoside-binding proteins, which are defined by their affinity for poly-*N*-acetyllactosamine-enriched glycoconjugates and sequence similarities in the carbohydrate recognition domain. By crosslinking specific glycoconjugates, different members of the galectin family behave as pro-inflammatory or anti-inflammatory agents, acting at different levels of acute and chronic inflammatory responses. Recent studies highlighted immunomodulatory roles for galectins *in vivo* in several experimental models of chronic inflammation, suggesting that these carbohydrate-binding proteins may be potential targets for the design of a novel generation of anti-inflammatory agents. In this study, we review recent advances on the role of galectins in the initiation, amplification and resolution of the inflammatory response. In particular, we examine the influence of individual members of this family in regulating cell adhesion, migration, chemotaxis, antigen presentation, immune cell activation and apoptosis. From a better understanding of the molecular basis of galectin-induced immune regulation, we may become able to exploit the potential of these sugar-binding proteins and their glycoligands as suitable therapeutic agents in acute and chronic inflammatory disorders.

Authors' affiliations:

N. Rubinstein,
J.M. Ilarregui,
M.A. Toscano,
G.A. Rabinovich

Division of Immunogenetics, Department of Microbiology, Hospital de Clínicas ''José de San Martín'', Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina

Correspondence to:
Dr Gabriel A. Rabinovich
Laboratorio de Inmunogenética
Hospital de Clínicas ''José de San Martín''
Universidad de Buenos Aires
Av. Córdoba 2351. 3er Piso (C1120)
Ciudad de Buenos Aires
Argentina
Tel.: +54-11-5950-8755/8756/8757
Fax: +54-11-5950-8758
e-mail: gabyrabi@ciudad.com.ar

Galectins are animal lectins defined by shared consensus amino acid sequences and affinity for β-galactose-containing oligosaccharides (1–4). This is an evolutionarily highly conserved family of proteins expressed by different immune cell types and homologues existing in mammals, birds, fishes as well as in lower organisms, such as nematodes and sponges, and even in microorganisms (1–5). In mammals, 14 members have been reported and a large number of additional members are identifiable in the published database (1).

Given the increased interest of immunologists in this field, the growing body of information raised during the past few years and the potential use of galectins as novel anti-inflammatory agents or targets for anti-inflammatory drugs, in this paper we review recent advances on the role of galectins in acute and chronic inflammation and the mechanisms involved in these processes.

Received 8 April 2004, accepted for publication 8 April 2004

doi: 10.1111/j.1399-0039.2004.00278.x

Tissue Antigens 2004: **64:** 1–12

Biochemistry and classification of galectins

Members of the galectin family are composed of one or two carbohydrate-recognition domains (CRDs) of approximately 130 amino acids (Fig. 1). Regarding the biochemical structure, some galectins contain one CRD (proto-type) and exist as monomers (galectin-5, -7 and -10) or dimers (galectin-1, -2, -11, -13 and -14), whereas other galectins, such as galectin-4, -6, -8, -9 and -12, contain two CRDs connected by a short linker region (tandem repeat). In contrast, galectin-3 uniquely occurs as a chimeric protein with one CRD and an additional non-lectin domain, which is involved in the oligomerization of this protein (Fig. 1). It has been suggested that multivalency of individual members of the galectin family and their crosslinking properties might determine different biological responses by inducing aggregation of specific cell-surface glycoreceptors, which – in many cases – are associated with different signal transduction events (4).

Carbohydrate specificity of galectins

Although most mammalian galectins bind preferentially to glycoconjugates containing the ubiquitous disaccharide *N*-acetyllactosamine [Gal β1→3Glc*N*Ac or Gal β1→4Glc*N*Ac], binding to individual lactosamine units is of relatively low affinity (Kd ≈ 1 μM), and it is the arrangement of lactosamine disaccharides in repeating chains (polylactosamine) that increases binding avidity. Moreover, detailed structural analysis of the CRDs suggests subtle differences in carbohydrate-binding specificities of individual members of this family (4). Whether subtle differences in saccharide specificity might be responsible for distinct biological responses to galectins remains to be elucidated.

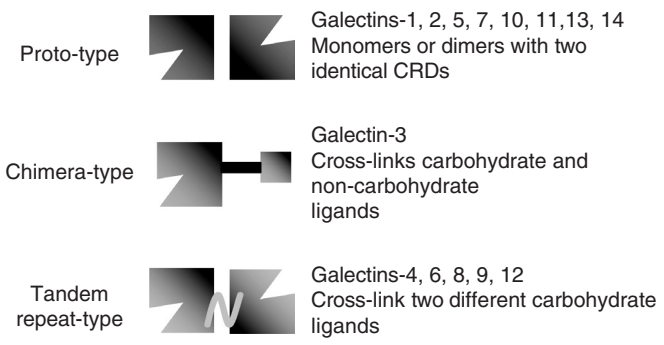

Fig. 1. **Schematic representation of the structure of different members of the galectin family**.

Subcellular localization and secretion

Although galectins are often reported to be present on cell surfaces or in the extracellular matrix (ECM), they lack recognizable secretion signal sequences and do not pass through the standard ER/Golgi pathway (1–4). Instead, most galectins have characteristics of typical cytoplasmic proteins, such as acetylated *N*-terminus, free sulfhydryls and lack of glycosylation. However, there is a strong experimental evidence that at least some galectins are, indeed, secreted by a novel mechanism distinct from classical vesicle-mediated exocytosis [similar to fibroblast growth factor and interleukin-1β (IL-1β)] (3).

Galectins in the physiology of the immune response

Extracellular and intracellular functions of galectins

Galectins have been shown to influence different functions involved in innate and adaptive immune responses (4). Once they are released into the extracellular medium, these β-galactoside-binding proteins may crosslink cell-surface glycoconjugates and induce signal transduction events through receptor clustering and formation of multivalent galectin–glycoprotein lattices on cell surfaces (4). Some of the extracellular functions reported for galectins include cell-growth regulation, activation, cell adhesion, chemotaxis and apoptosis (Fig. 2). In contrast, the intracellular effects of galectins do not appear to depend on the carbohydrate-binding activities of these endogenous lectins (4). Interestingly, recent observations suggest that the same galectin (for example, galectin-3) may exert different and contrasting effects whether they act extracellularly or intracellularly (6, 7).

Regulated expression of galectins within central and peripheral immune compartments

Galectins have a wide distribution in primary and secondary lymphoid organs and in circulating immune cells (4). Galectin-1 and -3 (the most widely studied) are expressed by thymic stromal cells (8, 9), activated T cells (10–12), activated B cells (13, 14) and inflammatory macrophages (Mϕs) (15–18). Interestingly, galectin expression is regulated according to the activation state of the cells (15–18).

Regulation of immune cell proliferation and apoptosis

In multicellular organisms, homeostasis is maintained through a balance between cell proliferation and cell death (3). In this sense, immune cells are subject to cell-death checkpoints at many stages

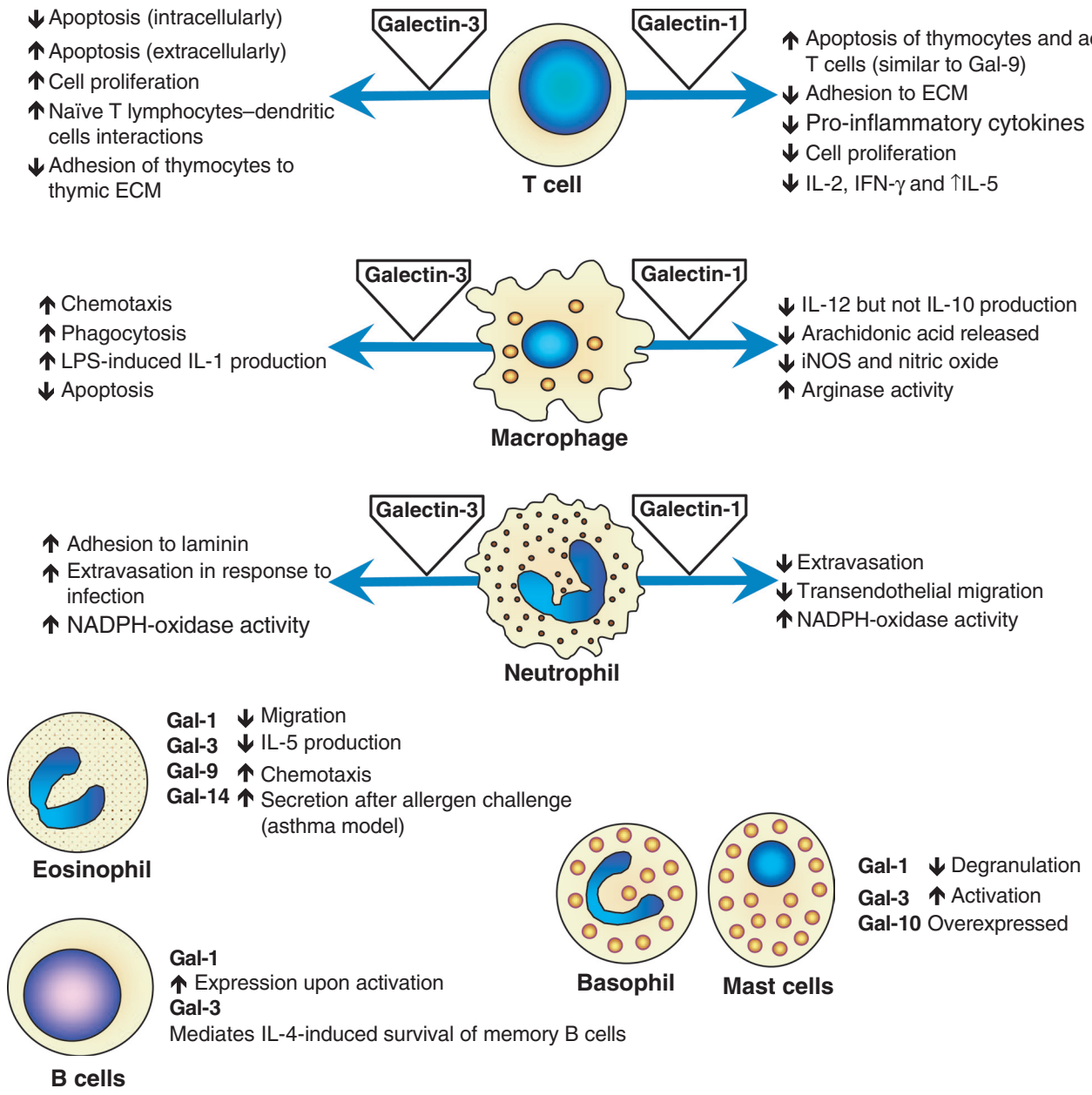

Fig. 2. **Effects of galectins in the physiology of different immune cell types**. Although the figure essentially illustrates the functions of galectin-1 (Gal-1) and galectin-3 (Gal-3), the other members of the family have been also shown to play key roles in immunomodulation.

during their lifespan to ensure proper development, maintain homeostasis and prevent disease. A distinct family of proteins regulates immune cell death. These include death-inducing ligands, death receptors and intracellular regulators of death pathways.

A growing body of evidence now indicates that galectin-1 induces cell-growth inhibition and cell-cycle arrest, and promotes apoptosis of activated, but not resting immune cells (10, 11, 17, 19, 20). Galectin-1 has shown specific growth inhibitory properties towards concanavalin-A (Con-A)-stimulated rat T cells (20), phytohemmaglutinin-activated (PHA) human T cells (10) and human alloreactive T cells (11). Further investigation revealed that galectin-1 induces apoptosis of peripheral T lymphocytes and developing thymocytes (17, 19, 20, 21). It has been shown that galectin-1 promotes apoptosis of immature cortical thymocytes *in vitro*, suggesting a potential role for this carbohydrate-binding protein in the maintenance of central tolerance (21). Similarly, mouse galectin-9 also induces apoptosis of thymocytes, in a lactose-inhibitable fashion (22). Recent evidence indicates that galectin-3 could act in a dual manner either protecting cells from apoptosis or stimulating cell death depending on whether the protein is found in the intracellular compartment (6) or it acts extracellularly (7).

Different cell-surface glycoconjugates on the surface of activated T cells appear to be primary receptors for galectins, including CD45, CD43, CD2, CD3, CD7 and CD29 (7, 23–25). Interestingly, galectin-1 binding to T cells results in a marked redistribution of many of these receptors into segregated membrane microdomains (23).

Recent evidence indicates that the regulated expression of glycosyltransferases during development and activation, creating *N*-acetyllactosamine ligands, may determine cell susceptibility to galectin-1 (26, 27). Galvan and colleagues (26) demonstrated that $CD45^+$ T cells lacking the core-2 β-1,6-*N*-acetylglucosaminyltransferase (C2GnT) are resistant to galectin-1-induced cell death. This enzyme is responsible for creating branched structures on *O*-glycans of T-cell-surface glycoproteins, such as CD45. Interestingly, an exciting study revealed that branched *O*-linked oligosaccharides ectopically expressed in C2GnT transgenic mice reduce primary T-cell immune responses *in vivo* (28). Whether galectin-1-induced apoptosis plays a role in the contraction of the T-cell repertoire and reduction of primary T-cell responses in transgenic C2GnT mice remains to be elucidated.

Other glycosyltransferases can also act to reduce galectin binding by indirectly or directly masking galectin saccharide ligands. In this sense, addition of α2,6-linked sialic acids to lactosamine units by the ST6Gal-I sialyltransferase has been shown to block galectin-1 binding due to interference of lactosamine insertion into the binding pocket of galectin-1 (27).

One concern regarding the pro-apoptotic activity of galectin-1 is that this effect has been demonstrated in most cases at relatively high concentrations (micromolar range) and it is uncertain whether high levels of soluble protein can be produced *in vivo*. Interestingly, recent evidence indicates that the amount of galectin-1 secreted by different cell types is sufficient to kill T cells, when galectin-1 is presented in the context of ECM glycoproteins (29). Moreover, the presence of galectin-1 in activated but not resting T cells (10) suggests a potential autocrine suicide mechanism to achieve homeostasis during the termination of an immune response.

On the other hand, CD7 has been identified as a critical receptor for galectin-1-induced apoptosis, and it has been recently demonstrated that $CD7^-$ T cells from patients with mycosis fungoides/Sezary syndrome are protected from galectin-1-triggered T-cell death (30, 31). Remarkably, Sezary cells in primary lesions showed a characteristic 'glycoepitope' with sialylated core 1 *O*-glycans, which confers resistance to galectin-1-induced apoptosis (31).

While these findings suggest a pivotal role for galectin-1 in the establishment and maintenance of T-cell tolerance and homeostasis *in vivo*, targeted disruption of the galectin-1 gene in knock-out mice results in the absence of major immunological abnormalities (2, 4). This finding suggests that other proteins (probably members of the galectin family) might potentially compensate for the absence of galectin-1.

Using a human allogeneic T-cell model, we have recently demonstrated that alternative mechanisms may operate to achieve T-cell hyporesponsiveness and immunosuppression as demonstrated by selective inhibition of IFN-γ production in the viable non-apoptotic T-cell population (11), while a major mechanism responsible for the anti-inflammatory effects of galectin-1 seems to be an induction of T-cell apoptosis. Furthermore, recent evidence suggests that exposure of activated leukocytes to dimeric galectin-1 may contribute to phagocytic recognition of these cells by inducing surface exposure of phosphotidylserine with no apparent signs of apoptosis (32).

The role of galectin-3 in the regulation of cell growth and apoptosis has been demonstrated in various cell types, using different experimental approaches. Most of the studies have focused on the intracellular functions of galectin-3 and reported a major role for this β-galactoside-binding protein in protecting cells from apoptosis and in promoting T-cell proliferation (4, 6, 12).

The first evidence indicating that galectin-3 might play a role in T-cell survival was the observation that human leukaemia T cells transfected with galectin-3 cDNA showed higher rates of proliferation and were protected from apoptosis induced by a wide variety of pro-apoptotic stimuli (6). Moreover, inhibition of galectin-3 by an oligonucleotide antisense specifically inhibited proliferation of anti-CD3-stimulated T cells (12). Furthermore, peritoneal Mϕs from galectin-3 knock-out mice displayed higher levels of apoptosis, compared to cells from wild-type mice, suggesting that this sugar-binding protein also protects Mϕs from cell death (33). An examination of the mechanisms responsible for this effect revealed that galectin-3 might act by preventing alterations of the mitochondrial membrane and formation of reactive oxygen species (34). Moreover, recent observations also indicate that post-translational modifications, such as galectin-3 phosphorylation, are essential for its anti-apoptotic activity (35).

In contrast to its intracellular anti-apoptotic activity, recent studies highlighted a novel role for extracellular galectin-3 in the promotion of T-cell apoptosis (7). Galectin-3-induced apoptosis involved binding of this protein to CD7 and CD29 (β1-integrin) on the T-cell surface, resulting in the activation of intracellular events, including cytochrome-c release and caspase-3 activation (7).

Other members of the galectin family have also been shown to modulate cell-cycle progression, proliferation and survival; for example, galectin-9 promotes apoptosis of immature thymocytes (22) and mature activated T cells through caspase-1 and calpain-dependent pathways (36). Galectin-7 is induced by the tumour-suppressor gene p53, and increases susceptibility of keratinocytes to ultraviolet-B-induced apoptosis (37). Gene profile experiments revealed that

galectin-7 functions intracellularly to induce apoptosis upstream of JNK activation and cytochrome-c release (38). Furthermore, galectin-8 has been shown to modulate tumour survival by binding to β-integrins (39) and galectin-12 has been shown to modulate cell-cycle progression and survival of adipocytes (40).

Taken together, these observations suggest that most members of the galectin family may influence, either positively or negatively, cell-cycle progression, proliferation and survival of different cell types.

Modulation of the interactions between T cells and antigen-presenting cells: implications for antigen presentation

Regarding a role of galectins in antigen presentation and T-cell activation, galectin-3 has been shown to positively contribute to cell interactions between dendritic cells and naïve T lymphocytes in T-cell-dependent areas of lymph nodes (41). In contrast, Demetriou and colleagues (42) reported that galectin-3 might play a potential role in restricting T-cell receptor (TCR) complex-initiated signal transduction. The authors hypothesize that galectin-3 forms multivalent complexes with *N*-glycans on TCR, thereby restraining the lateral mobility of TCR complexes (42). On the other hand, galectin-1 has been shown to antagonize IL-2 production by inducing partial TCR-ζ chain phosphorylation (43).

New insights into the role of galectins in immune cell development and differentiation

Pioneer studies suggested a role for galectin-1 in the development and maturation of T cell (8, 21). Galectin-1 is expressed by thymic epithelial cells, and induces apoptosis of immature cortical thymocytes (8, 21), suggesting a potential role of this protein in positive and/or negative selection within the thymic microenvironment.

Regarding the B-cell compartment, interesting findings indicated that galectin-1 acts as a stromal cell ligand of the pre-B-cell receptor (pre-BCR) implicated in synapse formation between pre-B and stromal cells (44). Moreover, we have recently demonstrated that galectin-3 is a critical mediator of B-cell differentiation and survival (14). Blockade of intracellular galectin-3 using an antisense strategy abrogated IL-4-induced survival of activated B cells, favouring the differentiation towards a plasma cell pathway. Moreover, B cells with restrained galectin-3 expression failed to downregulate the Blimp-1 transcription factor following IL-4 stimulation. *In vivo*, targeted inhibition of galectin-3 favoured plasma cell differentiation and increased the levels of immunoglobulin (Ig) production, resulting in parasite clearance and disease amelioration in an experimental model of *Trypanosoma cruzi* infection (14).

In an attempt to explore the potential role of galectins in myeloid cell differentiation, Abedin and colleagues (45) demonstrated, using an *in vitro* model, that galectin-10 mRNA is enhanced in the process of neutrophil and eosinophil differentiation, while galectin-3 expression is upregulated during monocyte differentiation and, surprisingly, galectin-9 expression decreases during the course of both monocyte and eosinophil differentiation.

Regulation of cell–cell and cell–matrix interactions

Adhesion and migration of cells through basement membranes and the ECM is a multistep process co-ordinated by receptors recognizing a mosaic of ECM glycoproteins, haptotactic chemokines and pro-inflammatory cytokines. It has been widely demonstrated that galectins bind to various cell adhesion molecules and ECM glycoproteins, including laminin and fibronectin, and modulate cell adhesion and migration of immune cells (46–48). We have demonstrated that galectin-1 at low concentrations (nanomolar range) provides a stop signal for T-cell adhesion through ECM glycoproteins, such as fibronectin and laminin, and abrogates the production of pro-inflammatory cytokines, such as tumour necrosis factor α (TNF-α) and interferon γ (IFN-γ), by activated T cells with no evidences of T-cell apoptosis (47). This observation supports the concept that this β-galactoside-binding protein might also exert its anti-inflammatory effects through alternative non-apoptotic mechanisms.

Regarding a role for galectin-3 in cell–cell and cell–matrix interactions, some opposing studies have been reported. While galectin-3 has been shown to positively contribute to cell interactions between dendritic cells and naïve T lymphocytes in lymph nodes (41), a recent study revealed that galectin−3 disrupts thymocyte interactions within the thymic microenvironment, thus acting as a de-adhesion molecule (9).

In an attempt to correlate the anti-apoptotic effect of galectin-3 with its cell adhesive properties, this β-galactoside-binding protein has been shown to inhibit apoptosis (anoikis) through a mechanism involving increased adhesiveness of cells to the ECM (49, 50). Galectin-3-overexpressing cells have significantly enhanced adhesion to laminin, fibronectin and vitronectin, an effect, which was related to an increased expression of $\alpha_4\beta_7$ integrins (49). In addition, the authors showed a remodelling of those cytoskeletal elements associated with cell spreading in cells transfected with galectin-3 cDNA. In particular, the actin microfilament network appeared to be differently organized and galectin-3-overexpressing cells were characterized by the absence of stress fibres and the presence of cell-surface F-actin-positive ruffles, known as markers of cell spreading (49). In this regard, we have found that inhibition of

T-cell adhesion by recombinant galectin-1 correlates with the ability of this molecule to block the re-organization of the activated cell's actin cytoskeleton (47).

Galectins as 'cytokine-like' molecules with sugar-binding activity

It has been proposed that galectins may act as 'cytokine-like' molecules, although it is still not clear whether they act as soluble cytokines or whether direct cell–cell or cell–matrix contact is required to exert their effects. In this sense, it has been documented that galectin-1 accumulates in stromal cells and ECM highlighting a critical role for ECM-associated galectin-1 in the initiation of T-cell death (29).

Similar to other cytokines that might influence a pro-inflammatory or anti-inflammatory cascade, galectin-1 has been shown to inhibit TNF-α and IFN-γ secretion from activated T cells *in vitro* (47). In addition, *in vivo* studies in experimental models of autoimmunity revealed the ability of galectin-1 to skew the balance towards a T2-type cytokine response by reducing the levels of IFN-γ, TNF-α, IL-2 and IL-12 and increasing the levels of IL-5 secretion (51–53). This polarizing effect was also observed following galectin-1 treatment in an experimental murine model of graft-versus-host disease (GVHD) (54).

In addition, we have demonstrated in an experimental model of *T. cruzi* infection that very low concentrations of galectin-1 were sufficient to downregulate critical mediators for parasite killing, such as IL-12 and nitric oxide, while this sugar-binding protein did not affect IL-10 production (18).

On the other hand, galectin-3 behaves in most cases as a 'pro-inflammatory cytokine', as has been demonstrated by the attenuated inflammatory response in galectin-3 knock-out mice (33). However, this lectin has been recently shown to suppress T2-type-mediated allergic inflammation by blocking IL-5 synthesis by human eosinophils and antigen-specific T-cell lines (55). In this context, it is interesting that galectin-1 is able to skew the balance of the immune response towards a T2-type cytokine profile, while galectin-3 downregulates IL-5-mediated T2-type responses.

Galectins as novel chemoattractants

Recent evidence indicates that galectins may also act as a new class of chemoattractants sharing many features with chemokines (56). In this sense, recombinant human galectin-3 promotes chemotaxis of human monocytes (56). The chemotactic activity of galectin-3 is inhibited by pertussis toxin, suggesting that a G-protein-coupled receptor may be involved in this process. *In vivo,* galectin-3 recruits monocytes, eosinophils and neutrophils in a mouse air-pouch model (56).

On the other hand, galectin-9 (also called ecalectin) is secreted by antigen-stimulated T lymphocytes and has been identified as a potent eosinophil-specific chemoattractant and a novel eosinophil-activating factor (57).

A critical role for galectins in innate immune responses

In addition to the role of galectins in adaptive immune responses, these sugar-binding proteins also modulate acute inflammatory processes and innate immunity (58–60). We have demonstrated that galectin-1 inhibits bee venom phospholipase A_2-induced oedema in a selective and dose-dependent manner, when pre-injected or co-injected together with the enzyme (58). In addition, we showed that this protein modulates alternative pathways of L-arginine metabolism in rat peritoneal Mϕs by inhibiting inducible nitric oxide synthase activity and promoting activation of the arginase pathway (60). Recent findings also indicate that galectin-1 may inhibit neutrophil chemotaxis and transendothelial migration (61).

As previously mentioned, in contrast to the anti-inflammatory effects of galectin-1, studies of induction of peritonitis in galectin-3-deficient mice provided significant support for the pro-inflammatory role of this lectin (33, 62). After intraperitoneal injection of thioglycolate, galectin-3 knock-out mice exhibited a significantly reduced number of recoverable granulocytes, compared to wild-type animals (33, 62). Interestingly, Karlsson and colleagues (63, 64) showed that both galectin-1 and -3 induce activation of the superoxide-producing NADPH-oxidase at similar levels in primed neutrophils.

In addition to the role of galectins in activating the respiratory burst, galectin-3 has been shown to modulate neutrophil adhesion to laminin (46). Moreover, recent findings showed that galectin-3 is upregulated in endothelial cells during *Streptococcus pneumoniae* infection (48) and that this protein mediates neutrophil adhesion to endothelial cells *in vitro.* More recently, Sano and colleagues highlighted a critical role for galectin-3 in phagocytosis by Mϕs (59). Compared with wild-type Mϕs, galectin-3-deficient cells exhibited reduced phagocytosis of Ig G-opsonized erythrocytes and apoptotic thymocytes both *in vitro* and *in vivo.*

Concerning the influence of other galectins in the modulation of innate immune response, recent findings indicate that galectin-8 is capable of modulating neutrophil functions related to transendothelial migration and microbial killing (65).

Galectins in concert: orchestrating and resolving the inflammatory response *in vivo*

Suppression of autoimmunity and chronic inflammation

A growing body of experimental evidence indicates that galectins may play a key role in the initiation, amplification or resolution of chronic inflammatory processes (4).

Galectin-1, a proto-type member of the galectin family, has been proposed to be, in general, a negative regulator of the immune response (4). *In vivo*, this β-galactoside-binding protein prevents the development of chronic inflammation and ameliorates the ongoing disease in experimental models of autoimmune encephalomyelitis (66), arthritis (51), colitis (52) and hepatitis (53) (Table 1). We have demonstrated, using gene and protein therapy strategies, that galectin-1 suppresses the chronic inflammatory response in collagen-induced arthritis in DBA/1 mice, an experimental model of rheumatoid arthritis (51). Injections of fibroblasts genetically engineered to secrete galectin-1 or continuous administration of recombinant galectin-1 after the onset of the disease abrogated clinical and histopathological manifestations of arthritis (51). Moreover, lymph node cells from galectin-1-treated mice were more susceptible to antigen-induced apoptosis than vehicle-treated mice.

Galectins as cytokine-like molecules with sugar-binding activity

As discussed in the section entitled, galectin-1 treatment induced a shift from a T1- towards a T2-polarized immune response, characterized by decreased IFN-γ and increased IL-5 production (51). The molecular mechanisms involved in galectin-1-induced T2 cytokine polarization are currently under study in our laboratory.

Interestingly, we also found that synovial tissue from patients with juvenile rheumatoid arthritis (JRA) has significantly less galectin-1, but more galectin-3 than normal synovial tissue (67). This regulated expression correlated with decreased mononuclear cell apoptosis in synovial tissue from these patients. In addition, recent evidence indicates that galectin-3 levels are elevated in sera and synovial fluids from patients with rheumatoid arthritis (RA) and that intracellular accumulation of galectin-3 can be enhanced by TNF-α (a typical pro-inflammatory cytokine) in RA synovial fibroblasts (68). A hypothetical model of a cross-talk between galectin-1 and galectin-3 in the context of an inflamed arthritic joint is illustrated in (Fig. 3).

The immunosuppressive activity of galectin-1 has also been demonstrated in Con-A-induced hepatitis, a T-cell-dependent model of liver injury in mice, characterized by the presence of infiltrating T cells in the liver (53). Galectin-1 prevented both liver injury and T-cell infiltration induced by Con-A, an effect associated with selective elimination of Con-A-activated T cells and suppression of Con-A-induced TNF-α and IFN-γ production (53). Furthermore, these findings have been recently confirmed in T1-mediated experimental colitis, an inflammatory bowel disease induced by intrarectal administration of 2,3,4-trinitrobenzene sulfonic acid in mice, demonstrating a striking improvement in the clinical and histopathological manifestations of the disease after prophylactic and therapeutic administration of recombinant galectin-1 (52).

In addition to its role in T1-mediated autoimmune processes, galectin-1 might also participate in autoantibody-mediated chronic inflammation, as a galectin-1 homologue purified from the fish *Electrophorus electricus* was able to prevent the development of experimental myasthenia gravis in rabbits (69). Furthermore, galectin-1, -3 and -9 were also tested for their ability to modulate the progression of nephrotoxic nephritis induced by injection of anti-glomerular basement membrane serum in Wistar Kyoto rats (70). Interestingly, the presence of anti-galectin-1 autoantibodies has been identified in several autoimmune and chronic inflammatory disorders, such as Chagas' cardiomiopathy (71), suggesting that they might play a role in the pathogenesis of human autoimmune diseases.

As previously mentioned, galectin-3 appears to be a positive regulator of inflammation *in vivo*. Inflammatory peritoneal cells from galectin-3-deficient mice showed significantly reduced levels of NF-κB activation (33). The role of other members of the galectin family in chronic inflammation *in vivo* still remains to be explored.

Galectins and allergic inflammation

Recent evidence indicates a role for galectins in T2-mediated allergic inflammation. As mentioned above, galectin-3 has been shown to downregulate IL-5 gene expression on eosinophilic cell lines and allergen-specific T cells (55). Consistently, Del Pozo and colleagues (72) recently found that galectin-3 gene delivery inhibits bronchial obstruction and inflammation in an experimental model of asthma through IL-5 downregulation in the lungs, suggesting that it could be a novel therapeutic approach for the treatment of allergic asthma.

Regarding the role of other members of the galectin family in allergic inflammation, galectin-1 has been recently shown to inhibit eosinophil migration *in vitro* (73) and degranulation of tissue mast cells *in vivo* in a model of acute inflammation (58). On the other hand, galectin-9 has been identified as a potent eosinophil-specific chemoattractant (57), suggesting a potential role for this protein in allergic reactions. In addition, Dunphy and colleagues (74) have identified a novel eosinophil-specific galectin (galectin-14) released into the lumen of the lungs in response to an allergenic challenge in a sheep asthma model.

Role of galectins in different models of experimental acute and chronic inflammation

Experimental model	Animal	Human correlate	Galectin	Treatment	Effects	Mechanisms
Experimental autoimmune encephalomyelitis (EAE)	Lewis rats	Multiple sclerosis	Gal-1	Prophylactic	Prevents induction of clinical and histological signs	Apparently by inducing mielin basic protein-dependent suppressor cells.
Collagen-induced arthritis (CIA)	DBA/1 mice	Rheumatoid arthritis	Gal-1	Therapeutic	Reduction of clinical score and histological signs	Increased susceptibility of T cells to AICD. Th2 polarization (IFN-γ, IL-5).
Experimental TNBS-induced colitis	BALBc mice	Crohn's disease	Gal-1	Prophylactic and therapeutic	Improvement of clinical and histological signs	Increased apoptosis of T cells in vivo and in vitro. Inhibition of pro-inflammatory cytokine production (IFN-γ, TNF-α, IL-1β, IL-12).
Experimental autoimmune myasthenia gravis (EAMG)	New Zealand rabbits	Myasthenia gravis	Electrolectin (Gal-1-like)	Prophylactic and therapeutic	Prevention of myasthenic symptoms and complete recovery	Decreased levels of anti-acetylcholine-receptor protein (AChR) antibodies.
Experimental nephrotoxic nephritis	Wistar kyoto rats	Human nephritis (Goodpasture's syndrome)	Gal-1, 3 and 9	Prophylactic	Reduced proliferation of glomerular cells and excretion of proteins	Inhibition of macrophage accumulation in renal glomeruli. Increased CD8+ T-cell apoptosis.
Con-A-induced hepatitis	BALBc mice	T-cell-mediated human liver disorders	Gal-1	Prophylactic	Prevention of liver injury and T-cell infiltration	Elimination of Con-A-activated T cells. Inhibition of TNF-α and IFN-γ production.
Phospholipase-A2-induced oedema	Wistar rats	Acute oedema	Gal-1	Prophylactic	Inhibition of acute inflammation	Reduced infiltration of polymorphonuclear neutrophils and reduced mast cells degranulation
Peritoneal inflammation	C57BL/6 Gal-3 knock-out mice	Peritonitis or other acute inflammatory responses	Gal-3	-	Attenuated inflammatory response	Decreased macrophage infiltration and NF-κB activation

AICD, activation-induced cell death; Con-A, concanavalin-A; IFN-γ, interferon-γ IL, interleukin; TNBS, trinitrobenzene sulfonic acid; TNF-α tumour necrosis factor-α

Table 1

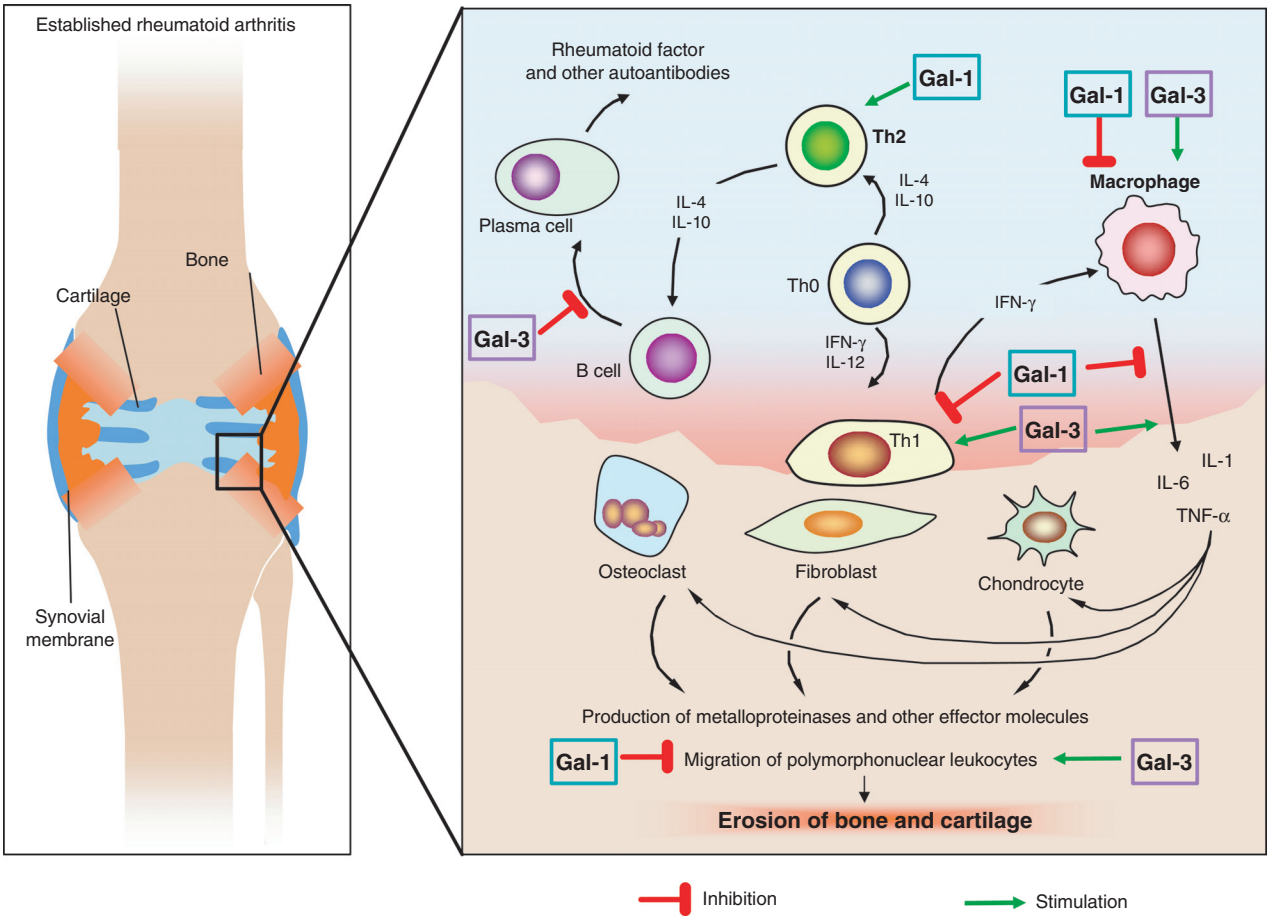

Fig. 3. **Galectins in immunopathology. Potential effects of galectin-1 (Gal-1) and galectin-3 (Gal-3) in the context of inflamed synovial tissue in rheumatoid arthritis (RA).**

Use of galectins as immunosuppressive agents in transplantation and GVHD

The ability of galectin-1 to suppress the allogeneic T-cell response through apoptotic and non-apoptotic mechanisms (11) suggests its potential use for immunosuppression in organ transplantation and GVHD.

In this context, Baum and colleagues (54) have recently explored the efficacy of galectin-1 treatment in a murine model of GVHD. They found that 68% of galectin-1-treated mice survived of GVHD, compared to 3% of vehicle-treated mice. Galectin-1 treatment significantly improved reconstitution of normal splenic architecture following haematopoietic stem-cell transplantation and, similar to its effects on autoimmune settings, this β-galactoside-binding protein reduced the production of T1-type cytokines (54).

Role of galectins during microbial infection

In order to study the effect of galectin-1 on the microbicidal activity of Mϕs, we used *T. cruzi* infection as a model of an intracellular infection (18). Galectin-1 induced a biphasic modulation of parasite replication and cell survival in Mϕs isolated from *T. cruzi*-infected mice or in cell lines infected *in vitro* with living trypomastigotes (18). While low concentrations of this protein increased parasite replication and did not affect cell survival, high inflammatory doses of galectin-1 promoted Mϕ apoptosis and decreased the number of intracellular amastigotes and extracellular trypomastigotes (18). Interestingly, low concentrations of this sugar-binding protein were sufficient to downregulate critical mediators for parasite killing, such as IL-12 and nitric oxide, while it did not affect IL-10 production.

Recently, Pelletier and colleagues (75, 76) proposed that galectin-3 and -9 recognize specific glycoepitopes in *Leishmania major* and can distinguish between *Leishmania major* and other species, suggesting that these galectins might act as immunomodulators that could influence the course of parasite-specific immune responses in leishmaniasis. Furthermore, recent findings indicate that altered glycosylation of T cells during human immunodeficiency type 1 (HIV-1) infection increases the susceptibility to galectin-1-induced cell death

(77), suggesting that this apoptotic pathway may contribute to HIV-1-induced immunosuppression.

Targeting cancer and metastasis

A correlation has been established between galectin expression in tumour tissues or tumour-associated stroma and disease progression in human and murine tumours, including breast cancer, prostate carcinomas, thyroid cancers, colon carcinoma, skin cancer, lymphoma, ovarian carcinomas and astrocitomas (78).

In fact, galectins have been implicated in many cellular functions that are crucial during cancer progression and metastasis (78), including homotypic cell aggregation, cell adhesion, cell migration, apoptosis and tumour cell proliferation. In addition, we have recently demonstrated that tumours can overwhelm T-cell effector functions through galectin-1-dependent mechanisms. By a combination of *in vitro* and *in vivo* experiments using knock-down transfectants, we established a link between galectin-1-mediated immunoregulation and its contribution to tumour-immune escape (79). Blockade of the inhibitory effects of galectin-1 within tumour tissue resulted in reduced tumour mass and enhanced tumour rejection, stimulating the generation of a potent tumour-specific T1-type response in syngeneic mice (79). Because human tumours express a complex pattern of galectin expression (80), future studies are warranted to dissect the functional role of individual members of the galectin family in tumour progression, tumour-immune escape and metastasis.

Conclusions and future perspectives

Recent advances in the understanding of the contribution of cell-surface glycoconjugates and carbohydrate-binding proteins to inflammatory processes have motivated the design of synthetic glycoconjugates or lectins as candidates for future generations of therapeutic drugs.

The evidences presented in this study illustrate the importance of different members of the galectin family in the regulation of innate and adaptive immune responses. This growing family of endogenous lectins plays crucial roles in cell-growth regulation, activation, cell adhesion, cytokine production, chemotaxis and apoptosis. However, despite considerable progress in elucidating galectin functions within the immune system, future comparative studies among different galectins will be necessary to address the precise role of individual members of the family and their functional redundancy. Moreover, future work should be performed to elucidate the precise mechanisms involved in the immunoregulatory properties of this protein family at the cellular and molecular levels and to examine carefully the immune system of galectin knock-out mice and their response to different inflammatory, autoimmune or allergic stimuli. It is intriguing that some members of the family will act in the resolution step of the inflammatory responses, whereas the other members with similar carbohydrate specificity and conserved amino acid sequence will contribute to the initiation and amplification of the inflammatory response. However, it has been recently realized that the same galectin might exert pro- or anti-inflammatory effects depending on multiple factors, including subcellular compartmentalization, activation state of target cells and concentrations tested.

References

1. Cooper DNW. Galectinomics: finding themes in complexity. *Biochim Biophys Acta* 2002: **1572**: 209–31.
2. Leffler H, Carlsson S, Hedlund M, Qian Y, Poirier F. Introduction to galectins. *Glycoconj J* 2004: **19**: 433–40.
3. Rabinovich GA. Galectins: an evolutionarily conserved family of animal lectins with multifunctional properties; a trip from the gene to clinical therapy. *Cell Death Diff* 1999: **6**: 711–21.
4. Rabinovich GA, Baum LG, Tinari N et al. Galectins and their ligands: amplifiers, silencers or tuners of the inflammatory response. *Trends Immunol* 2002: **23**: 313–20.
5. Ahmed H, DU SJ, O'Leary N, Vasta GR. Biochemical and molecular characterization of galectins from zebrafish (Danio rerio): notochord-specific expression a prototype galectin during early embryogenesis. *Glycobiol* 2004: **14**: 219–32.
6. Yang RY, Hsu DK, Liu FT. Expression of galectin-3 modulates T cell growth and apoptosis. *Proc Natl Acad Sci USA* 1996: **93**: 6737–42.
7. Fukumori T, Takenaka Y, Yoshii T et al. CD29 and CD7 mediate galectin-3-induced type II T-cell apoptosis. *Cancer Res* 2003: **63**: 8302–11.
8. Baum LG, Pang M, Perillo NL et al. Human thymic epithelial cells express an endogenous lectin, galectin-1, which binds to core 2 *O*-glycans on thymocytes and T lymphoblastoid cells. *J Exp Med* 1995: **181**: 877–87.
9. Villa-Verde DM, Silva-Monteiro E, Jasiulionis MG et al. Galectin-3 modulates carbohydrate-dependent thymocyte interactions with the thymic microenvironment. *Eur J Immunol* 2002: **32**: 1434–44.
10. Blaser C, Kaufmann M, Muller C et al. β-galactoside binding protein secreted by activated T cells inhibits antigen-induced proliferation of T cells. *Eur J Immunol* 1998: **28**: 2311–9.
11. Rabinovich GA, Ramhorst RE, Rubinstein N et al. Induction of allogeneic T-cell hyporesponsiveness by galectin-1-mediated apoptotic and non-apoptotic mechanisms. *Cell Death Diff* 2002: **9**: 661–70.

12. Joo HG, Goedegebuure PS, Sadanaga N, Nagoshi M, von Bernstorff M, Eberlein TJ. Expression and function of galectin-3, a beta-galactoside-binding protein in activated T lymphocytes. *J Leukoc Biol* 2001: **69**: 555–64.
13. Zúñiga EI, Rabinovich GA, Iglesias MM, Gruppi A. Regulated expression of galectin-1 during B cell activation and implications for T-cell apoptosis. *J Leukoc Biol* 2001: **70**: 73–9.
14. Acosta-Rodríguez EV, Montes CL, Motran CC et al. Galectin-3 mediates interleukin-4-induced survival and differentiation of B cells. Functional cross-talk and implications during *Trypanosoma cruzi* infection. *J Immunol* 2004: **172**: 493–502.
15. Sato S, Hughes RC. Regulation of secretion and surface expression of Mac-2, a galactoside-binding protein in macrophages. *J Biol Chem* 1994: **269**: 4424–30.
16. Rabinovich GA, Castagna LF, Landa CA, Riera CM, Sotomayor CE. Regulated expression of a 16 kDa galectin-like protein in activated rat macrophages. *J Leukoc Biol* 1996: **59**: 363–70.
17. Rabinovich GA, Iglesias MM, Modesti NM et al. Activated rat macrophages produce a galectin-1-like protein that induces apoptosis of T cells: biochemical and functional characterization. *J Immunol* 1998: **160**: 4831–40.
18. Zuñiga EI, Gruppi A, Hirabayashi J, Kasai KI, Rabinovich GA. Regulated expression and effect of galectin-1 on *Trypanosoma cruzi*-infected macrophages: modulation of microbicidal activity and survival. *Infect Immun* 2001: **69**: 6804–12.
19. Perillo NL, Pace KE, Seilhamer JJ, Baum LG. Apoptosis of T cells mediated by galectin-1. *Nature* 1995: **378**: 736–9.
20. Rabinovich GA, Modesti NM, Castagna LF, Landa CA, Riera CM, Sotomayor CE. Specific inhibition of lymphocyte proliferation and induction of apoptosis by CLL-I, a β-galactoside-binding lectin. *J Biochem* 1997: **122**: 365–73.
21. Perillo NL, Uittenbogaart CH, Nguyen JT, Baum LG. Galectin-1, an endogenous lectin produced by thymic epithelial cells, induces apoptosis of human thymocytes. *J Exp Med* 1997: **97**: 1851–8.
22. Wada J, Ota K, Kumar A, Wallner EI, Kanwar YS. Developmental regulated expression and apoptotic potential of galectin-9, a beta-galactoside-binding lectin. *J Clin Invest* 1997: **99**: 2452–61.
23. Pace KE, Lee C, Stewart PL, Baum LG. Restricted receptor segregation into membrane microdomains occurs on human T cells during apoptosis induced by galectin-1. *J Immunol* 1999: **163**: 3801–11.
24. Walzel H, Blach M, Hirabayashi J, Kasai KI, Brock J. Involvement of CD2 and CD3 in galectin-1-induced signaling in human Jurkat T cells. *Glycobiology* 2000: **10**: 131–40.
25. Fouillit M, Joubert-Caron R, Poirier F et al. Regulation of CD45 signaling by galectin-1 in Burkitt lymphoma B cells. *Glycobiology* 2000: **10**: 413–9.
26. Galvan M, Tsuboi S, Fukuda M, Baum LG. Expression of a specific glycosyltransferase enzyme regulates T cell death mediated by galectin-1. *J Biol Chem* 2000: **275**: 16730–7.
27. Amano M, Galvan M, He J, Baum LG. The ST6Gal I sialyltransferase selectively modifies N-glycans on CD45 to negatively regulate galectin-1-induced CD45 clustering, phosphatase modulation and T cell death. *J Biol Chem* 2003: **278**: 7469–75.
28. Tsuboi S, Fukuda M. Branched *O*-linked oligosaccharide ectopically expressed in transgenic mice reduces primary T-cell immune responses. *EMBO J* 1997: **16**: 6364–73.
29. He J, Baum LG. Presentation of galectin-1 by extracellular matrix triggers T-cell death. *J Biol Chem* 2004: **279**: 4705–12.
30. Rappl G, Abken H, Muche JM et al. $CD4^+$ $CD7^-$ leukemic T cells from patients with Sezary syndrome are protected from galectin-1-triggered T cell death. *Leukemia* 2002: **16**: 840–5.
31. Roberts AA, Amano M, Felten C et al. Galectin-1-mediated apoptosis in mycosis fungoides: the roles of CD7 and cell surface glycosylation. *Mod Pathol* 2003: **16**: 543–51.
32. Dias-Baruffi M, Zhu H, Cho M, Karmakar S, McEver RP, Cummings RD. Dimeric galectin-1 induces surface exposure of phosphatidylserine and phagocytic recognition of leukocytes without inducing apoptosis. *J Biol Chem* 2003: **278**: 41282–93.
33. Hsu DK, Yang RY, Yu L et al. Targeted disruption of galectin-3 gene results in attenuated peritoneal inflammatory responses. *Am J Pathol* 2000: **156**: 1073–83.
34. Matarrese P, Tinari N, Semeraro ML, Natoli C, Iacobelli S, Malorni W. Galectin-3 overexpression protects from cell damage and death by influencing mitochondrial homeostasis. *FEBS Lett* 2000: **473**: 311–5.
35. Yoshii T, Fukumori T, Honjo Y, Inohara H, Kim HR, Raz A. Galectin-3 phosphorylation is required for its anti-apoptotic function and cell cycle arrest. *J Biol Chem* 2002: **277**: 6852–7.
36. Kashio Y, Nakamura K, Abedin MJ et al. Galectin-9 induces apoptosis through the calcium-calpain-caspase 1 pathway. *J Immunol* 2003: **170**: 3631–6.
37. Bernerd F, Sarasin A, Magnaldo T. Galectin-7 overexpression is associated with the apoptotic process in UVB-induced sunburn keratinocytes. *Proc Natl Acad Sci USA* 1999: **96**: 11329–34.
38. Kuwabara I, Kuwabara Y, Yang RY et al. Galectin-7 (PIG1) exhibits pro-apoptotic function through JNK activation and mitochondrial cytochrome c release. *J Biol Chem* 2002: **277**: 3487–97.
39. Hadari YR, Arbel-Goren R, Levy Y et al. Galectin-8 binding to integrins inhibits cell adhesion and induces apoptosis. *J Cell Sci* 2000: **113**: 2385–97.
40. Yang RY, Hsu DK, Yu L, Ni J, Liu F-T. Cell cycle regulation by galectin-12, a new member of the galectin superfamily. *J Biol Chem* 2001: **276**: 20252–60.
41. Swarte VV, Mebius RE, Joziasse DH, van den Eijnden DH, Kraal G. Lymphocyte triggering via L-selectin leads to enhanced galectin-3-mediated binding to dendritic cells. *Eur J Immunol* 1998: **28**: 2846–71.
42. Demetriou N, Granovsky M, Quaggin S, Dennis JW. Negative regulation of T-cell activation and autoimmunity by Mgat5 N-glycosylation. *Nature* 2001: **409**: 733–9.
43. Chung CD, Patel VP, Moran M, Lewis LA, Miceli MC. Galectin-1 induces partial TCR ζ-chain phosphorylation and antagonizes processive TCR signal transduction. *J Immunol* 2000: **165**: 3722–9.
44. Gauthier L, Rossi B, Roux F, Termine E, Schiff C. Galectin-1 is a stromal cell ligand of the pre-B cell receptor (BCR) in synapse formation between pre-B and stromal cells and in pre-BCR triggering. *Proc Natl Acad Sci USA* 2002: **99**: 13014–9.
45. Abedin MJ, Kashio Y, Seki M, Nakamura K, Hirashima M. Potential roles of galectins in myeloid differentiation into three different lineages. *J Leukoc Biol* 2003: **73**: 650–6.
46. Kuwabara I, Liu F-T. Galectin-3 promotes adhesion of human neutrophils to laminin. *J Immunol* 1996: **156**: 3939–44.
47. Rabinovich GA, Ariel A, Hershkoviz R, Hirabayashi J, Kasai KI, Lider O. Specific inhibition of T-cell adhesion to extracellular matrix and pro-inflammatory cytokine secretion by human recombinant galecitn-1. *Immunology* 1999: **97**: 100–6.
48. Sato S, Ouellet N, Pelletier I, Simard M, Rancourt A, Bergeron MG. Role of galectin-3 as an adhesion molecule for neutrophil extravasation during Streptococcal Pneumonia. *J Immunol* 2002: **168**: 1813–22.
49. Matarrese P, Fusco O, Tinari N et al. Galectin-3 overexpression protects from apoptosis by improving cell adhesion properties. *Int J Cancer* 2000: **85**: 545–54.

50. Kim HR, Lin HM, Birilan H, Raz A. Cell cycle arrest and inhibition of anoikis by galectin-3 in human breast epithelial cells. *Cancer Res* 1999: **59**: 4148–54.
51. Rabinovich GA, Daly G, Dreja H et al. Recombinant galectin-1 and its genetic delivery suppress collagen-induced arthritis via T cell apoptosis. *J Exp Med* 1999: **190**: 385–97.
52. Santucci L, Fiorucci S, Rubinstein N et al. Galectin-1 suppresses experimental colitis in mice. *Gastroenterology* 2003: **124**: 1381–94.
53. Santucci L, Fiorucci S, Cammilleri F, Servillo G, Federici B, Morelli A. Galectin-1 exerts immunomodulatory and protective effects on concanavalin A-induced hepatitis in mice. *Hepatology* 2000: **31**: 399–406.
54. Baum LG, Blackall DP, Arias-Magallano S et al. Amelioration of graft versus host disease by galectin-1. *Clin Immunol* 2003: **109**: 295–307.
55. Cortegano I, del Pozo V, Cardaba B et al. Galectin-3 down-regulates IL-5 gene expression on different cell types. *J Immunol* 1998: **161**: 385–9.
56. Sano H, Hsu DK, Yu L et al. Human galectin-3 is a novel chemoattractant for monocytes and macrophages. *J Immunol* 2000: **165**: 2156–64.
57. Matsumoto R, Hirashima M, Kita H, Gleich GJ. Biological activities of ecalectin: a novel eosinophil-activating factor. *J Immunol* 2002: **168**: 1961–7.
58. Rabinovich GA, Sotomayor CE, Riera CM, Bianco I, Correa SG. Evidence of a role for galectin-1 in acute inflammation. *Eur J Immunol* 2000: **30**: 1331–9.
59. Sano H, Hsu DK, Apgar JR et al. Critical role of galectin-3 in phagocytosis by macrophages. *J Clin Invest* 2003: **112**: 389–97.
60. Correa SG, Sotomayor CE, Aoki MP, Maldonado CA, Rabinovich GA. Opposite effects of galectin-1 on alternative metabolic pathways of L-arginin in resident, inflammatory and activated macrophages. *Glycobiology* 2003: **13**: 119–28.
61. La M, Cao TV, Cerchiaro G et al. A novel biological activity for galectin-1: inhibition of leukocyte–endothelial cell interactions in experimental inflammation. *Am J Pathol* 2003: **163**: 1505–15.
62. Colnot C, Ripoche MA, Milon G, Montagutelli X, Crocker PR, Poirier F. Maintenance of granulocyte numbers during acute peritonitis is defective in galectin-3-null mutant mice. *Immunology* 1998: **94**: 290–6.
63. Karlsson A, Follin P, Leffler H, Dahigren C. Galectin-3 activates the NADPH oxidase in exudated but not peripheral blood neutrophils. *Blood* 1998: **91**: 3430–8.
64. Almkvist J, Dahlgren C, Leffler H, Karlsson A. Activation of the neutrophil nicotinamide adenine dinucleotide phosphatase oxidase by galectin-1. *J Immunol* 2002: **168**: 4034–41.
65. Nishi N, Shoji H, Seki M et al. Galectin-8 modulates neutrophil function via interaction with integrin alphaM. *Glycobiology* 2003: **13**: 755–63.
66. Offner H, Celnik B, Bringman T, Casentini-Borocz D, Nedwin GE, Vanderbark A. Recombinant human β-galactoside-binding lectin suppresses clinical and histological signs of experimental autoimmune encephalomyelitis. *J Neuroimmunol* 1990: **28**: 177–84.
67. Harjacek M, Díaz-Cano S, Miguel M, Wolfe H, Maldonado C, Rabinovich GA. Expression of galectins-1 and -3 correlates with defective mononuclear cell apoptosis in patients with juvenile rheumatoid arthritis. *J Rheumatol* 2001: **28**: 1914–22.
68. Ohshima S, Kuchen S, Seemayer CA et al. Galectin 3 and its binding protein in rheumatoid arthritis. *Arthritis Rheum* 2003: **48**: 2788–95.
69. Levy G, Tarrab-Hazdai R, Teichberg VI. Prevention and therapy with electrolectin of experimental autoimmune myasthenia gravis in rabbits. *Eur J Immunol* 1983: **13**: 500–7.
70. Tuchiyama Y, Wada J, Zhang H et al. Efficacy of galectins in the amelioration of nephrotoxic serum nephritis in Wistar Kyoto rats. *Kidney Int* 1999: **58**: 1941–52.
71. Giordanengo L, Gea S, Barbieri G, Rabinovich GA. Anti-galectin-1 autoantibodies in human *Trypanosoma cruzi* infection: differential expression of this β-galactoside-binding protein in cardiac Chagas' disease. *Clin Exp Immunol* 2001: **124**: 266–73.
72. Del Pozo V, Rojo M, Rubio ML et al. Gene therapy with galectin-3 inhibits bronchial obstruction and inflammation in antigen-challenged rats through interleukin-5 gene downregulation. *Am J Respir Crit Care Med* 2002: **166**: 732–7.
73. Delbrouck C, Doyen I, Belot N et al. Galectin-1 is overexpressed in nasal polyps under budesonide and inhibits eosinophil migration. *Lab Invest* 2002: **82**: 147–58.
74. Dunphy JL, Barcham GJ, Bischof RJ, Young AR, Nash A, Meeusen EN. Isolation and characterization of a novel eosinophil-specific galectin released into the lungs in response to allergen challenge. *J Biol Chem* 2002: **277**: 14916–24.
75. Pelletier I, Sato S. Specific recognition and cleavage of galectin-3 by Leishmania major through species-specific polygalactose epitope. *J Biol Chem* 2002: **277**: 17663–70.
76. Pelletier I, Hashidate T, Urashima T et al. Specific recognition of Leishmania major poly-beta-galactosyl epitopes by galectin-9: possible implication of galectin-9 in interaction between L. major and host cells. *J Biol Chem* 2003: **278**: 22223–30.
77. Lanteri M, Giordanengo V, Hiraoka N et al. Altered T cell surface glycosylation in HIV-1 infection results in increased susceptibility to galectin-1-induced cell death. *Glycobiology* 2003: **13**: 909–18.
78. Van den Brüle F, Califice S, Castronovo V. Expression of galectins in cancer: a critical review. *Glycoconj J* 2004: **19**: 537–42.
79. Rubinstein N, Alvarez M, Zwirner NW et al. Targeted inhibition of galectin-1 gene expression in tumor cells results in heightened T cell-mediated rejection: a potential mechanism of tumor-immune privilege. *Cancer Cell* 2004: **5**: 241–51.
80. Lahm H, André S, Hoeflich A et al. Comprehensive galectin fingerprinting in a panel of 61 human tumor cell lines by RT-PCR and its implications for diagnostic and therapeutic procedures. *J Cancer Res Clin Oncol* 2001: **127**: 375–86.