The Journal of Immunology

Galectin-1: A Jack-of-All-Trades in the Resolution of Acute and Chronic Inflammation

Victoria Sundblad, Luciano G. Morosi, Jorge R. Geffner and Gabriel A. Rabinovich

J Immunol 2017; 199:3721-3730; ;
doi: 10.4049/jimmunol.1701172
http://www.jimmunol.org/content/199/11/3721

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

Brief Reviews

The Journal of Immunology

Galectin-1: A Jack-of-All-Trades in the Resolution of Acute and Chronic Inflammation

Victoria Sundblad,[*,1] Luciano G. Morosi,[*,†,1] Jorge R. Geffner,[‡,§] and Gabriel A. Rabinovich[*,†]

Regulatory signals provide negative input to immunological networks promoting resolution of acute and chronic inflammation. Galectin-1 (Gal-1), a member of a family of evolutionarily conserved glycan-binding proteins, displays broad anti-inflammatory and proresolving activities by targeting multiple immune cell types. Within the innate immune compartment, Gal-1 acts as a resolution-associated molecular pattern by counteracting the synthesis of proinflammatory cytokines, inhibiting neutrophil trafficking, targeting eosinophil migration and survival, and suppressing mast cell degranulation. Likewise, this lectin controls T cell and B cell compartments by modulating receptor clustering and signaling, thus serving as a negative-regulatory checkpoint that reprograms cellular activation, differentiation, and survival. In this review, we discuss the central role of Gal-1 in regulatory programs operating during acute inflammation, autoimmune diseases, allergic inflammation, pregnancy, cancer, and infection. Therapeutic strategies aimed at targeting Gal-1–glycan interactions will contribute to overcome cancer immunosuppression and reinforce antimicrobial immunity, whereas stimulation of Gal-1–driven immunoregulatory circuits will help to mitigate exuberant inflammation. *The Journal of Immunology*, **2017, 199: 3721–3730.**

Resolution of immune responses involves the interplay between anti-inflammatory and proresolving mediators that are rapidly released at times of cellular stress and tissue injury to counterbalance exuberant inflammation, mitigate collateral tissue damage, and orchestrate immune cell homeostasis (1). These include immunosuppressive cytokines (IL-10, TGF-β_1, IL-35), anti-inflammatory neuropeptides (vasoactive intestinal peptide, neuropeptide Y), bioactive lipid molecules (lipoxins, resolvins, protectins), steroid hormones (glucocorticoids), and resolution-associated molecular patterns (RAMPs), including glucose-regulated protein 78, heat shock protein 10, heat shock protein 27, and αβ-crystallin, which together counteract the proinflammatory effects triggered by danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (2, 3).

Galectins, a family of soluble β-galactoside–binding proteins widely expressed at sites of inflammation, infection, and tumor growth, have emerged as a new class of DAMPs or RAMPs that serve to amplify or resolve inflammatory responses (4, 5). Based on their architecture, galectins have been grouped into three subfamilies: "proto-type" galectins, consisting of a single polypeptide chain with one carbohydrate recognition domain (CRD) that can dimerize (galectin-1 [Gal-1], -2, -5, -7, -10, -11, -13, -14, and 15); "tandem repeat-type" galectins composed of a single polypeptide chain exhibiting two CRDs connected by a linker peptide (Gal-4, -6, -8, -9, and -12); and the "chimera-type" Gal-3, which consists of one C-terminal CRD domain linked to an N-terminal domain (6). Once synthesized, galectins may remain inside the cell and control intracellular processes, or they may be released to the extracellular space through a nonconventional pathway that remains unknown (7–10). Whereas one-CRD galectins can dimerize via the back sides of their CRDs, chimera-type Gal-3 can pentamerize via its nonlectin N-terminal domain, and tandem-repeat galectins can oligomerize (11). The formation of multivalent galectin–glycan complexes contributes to the assembly and organization of cell surface receptors, controlling their segregation, internalization, and signaling (6). In fact, galectins can interact with a wide range of glycosylated receptors and trigger distinct signaling programs, including immune cell activation, differentiation, trafficking, and survival (6). Although some members of the galectin family act primarily as proinflammatory mediators, others display broad anti-inflammatory activities; yet, in most circumstances, stimulatory or inhibitory effects vary according to different

*Laboratorio de Inmunopatología, Instituto de Biología y Medicina Experimental, Consejo de Investigaciones Científicas y Técnicas, C1428 Buenos Aires, Argentina; †Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, C1428 Buenos Aires, Argentina; ‡Departamento de Microbiología, Facultad de Medicina, Universidad de Buenos Aires, C1405 Buenos Aires, Argentina; and §Instituto de Investigaciones Biomédicas en Retrovirus y SIDA, Consejo de Investigaciones Científicas y Técnicas, Universidad de Buenos Aires, C1405 Buenos Aires, Argentina

[1]V.S. and L.G.M. contributed equally to this work.

ORCIDs: 0000-0002-7011-6821 (V.S.); 0000-0002-4649-6473 (L.G.M.).

Received for publication August 15, 2017. Accepted for publication October 10, 2017.

Work in G.A.R.'s laboratory is supported by grants from Agencia Nacional de Promoción Científica y Tecnológica (Argentina) (PICT 2012-2440 and PICT 2014-3687), the Kenneth Rainin Foundation, the University of Buenos Aires (2013–2016), Fundación Bunge y Born, and Fundación Sales.

Address correspondence and reprint requests to Dr. Gabriel A. Rabinovich, Instituto de Biología y Medicina Experimental, Consejo de Investigaciones Científicas y Técnicas, Vuelta de Obligado 2490, C1428 Buenos Aires, Argentina. E-mail address: gabyrabi@gmail.com

Abbreviations used in this article: CRD, carbohydrate recognition domain; DAMP, danger-associated molecular pattern; DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; Gal-1, galectin-1; IBD, inflammatory bowel disease; LacNAc, *N*-acetyl-lactosamine; *Lgals1*$^{-/-}$, Gal-1 deficient; RAMP, resolution-associated molecular pattern; T1D, type 1 diabetes; Treg, regulatory T cell; WT, wild-type.

tissue contexts, intracellular or extracellular localization of these proteins, pathologic conditions, and spatiotemporal expression of other regulatory programs (6, 11). Illustrating this concept, Gal-3 and Gal-9 have been proposed to act as alarmins or DAMPs that orchestrate inflammatory responses during sepsis, parasite infection, and neuroinflammation (5, 12–14), yet these lectins may exhibit immune-inhibitory activities in tumor microenvironments (15, 16).

Gal-1: a sweet checkpoint in the resolution of inflammatory responses

Gal-1, the first galectin identified, acts typically as a proresolving mediator by repressing a number of innate and adaptive immune programs (4). From a structural standpoint, Gal-1 is composed of two subunits of 14.5 kDa (135 aa) present in a dynamic dimerization equilibrium (4). Because of an unusual number of six cysteine residues, this lectin is highly sensitive to oxidative inactivation, which limits its biological activity (17). Although typically conceived as independent processes, studies suggested that these mechanisms could be interconnected as dimerization favors ligand binding, which protects Gal-1 from oxidative inactivation (18).

Gal-1 recognizes multiple galactose-β1-4–*N*-acetyl-glucosamine (*N*-acetyl-lactosamine [LacNAc]) units present on the branches of *N*- or *O*-linked glycans on diverse cell surface receptors, including CD45, CD43, CD69, pre-BCR, and vascular endothelial growth factor R2 (11, 19–21). Different glycosyltransferases act in concert to create Gal-1–specific ligands, including *N*-acetylglucosaminyltransferase 5 (MGAT5), an enzyme that generates β1,6-*N*-acetylglucosamine–branched complex *N*-glycans and the core-2 β1-6–*N*-acetylglucosaminyltransferase 1 (C2GNT1), an enzyme that catalyzes branching of core-2 *O*-glycans. Conversely, Gal-1 binding is thwarted when LacNAc is modified by α2,6-linked sialic acid incorporated by the α2,6 sialyltransferase 1 (ST6GAL1) (6). Thus, sensitivity to Gal-1 is influenced by intrinsic and extrinsic factors, including dimerization equilibrium, redox status, and the regulated activity of glycosyltransferases responsible for creating or hindering specific glycan structures on target cells (6).

Within the immune system, Gal-1 is synthesized and secreted by a wide range of cells, including activated T and B cells (22, 23), macrophages (24), Foxp3$^+$ regulatory T cells (Tregs) (25, 26), tolerogenic dendritic cells (DCs) (27, 28), γδ T cells (29), microglia (30), and myeloid-derived suppressor cells (29). Remarkably, Gal-1 expression is prominent in immune-privileged sites, such as placenta (31, 32), testis (33, 34), and the eye (35), and is significantly up- or downmodulated in inflammatory conditions, including microbial infection (36–38), autoimmunity (27, 39), allergy (40, 41), cancer (19, 29, 42–44), reproductive disorders (31, 32, 45, 46), neurodegenerative diseases (30), and myocardial infarction (47). Interestingly, in experimental models, Gal-1 expression peaks during the recovery phase of autoimmune disease (27, 30), indicating a major role for this lectin during resolution of inflammation. In this article, we focus on the proresolving roles of Gal-1 during acute and chronic inflammatory responses (Fig. 1) and discuss its therapeutic potential in a broad range of physiologic and pathologic conditions.

Gal-1 in acute inflammation: portrait of a RAMP

Three major steps, namely initiation, amplification, and resolution, are involved in acute inflammation (48). Unresolved inflammation may lead to several diseases, such as atherosclerosis, asthma, fibrosis, and metabolic diseases (49). A large body of evidence suggests that Gal-1 mediates anti-inflammatory actions, as well as contributes to actively resolve acute inflammation. Exogenous Gal-1 markedly inhibited acute inflammation induced by administration of phospholipase A2 or carrageenan and attenuated neutrophil infiltration (50–53). However, a low degree of inflammation and leukocyte infiltration was observed in Gal-1–deficient (*Lgals1*$^{-/-}$) mice in a second phase (48–96 h), but not in the first phase (24 h), of edema (53), suggesting distinct roles for endogenous versus exogenous Gal-1 during different stages of the inflammatory response. Mechanistically, exogenous Gal-1 inhibits activation, chemotaxis, and extravasation of neutrophils induced by inflammatory stimuli (52, 53). Moreover, it also promotes cell surface phosphatidylserine exposure, favoring phagocytic removal of viable neutrophils (54). In contrast, this lectin stimulates activation and migration of resting neutrophils (55). Thus, the cellular activation status, which leads to different glycosylation or signaling profiles, might dictate Gal-1 function.

With regard to macrophages, cooperative partners of neutrophils in innate immunity, numerous studies demonstrate that Gal-1 promotes the acquisition of an anti-inflammatory and proresolving profile. By controlling L-arginine metabolism, either by reducing the production of NO or favoring the arginase pathway, Gal-1 promotes differentiation of macrophages into an M2 profile (56). In *Trypanosoma cruzi*–infected macrophages, Gal-1 inhibited IL-12 and NO production, favoring parasite replication (57). Moreover, through inhibition of MHC class II and FcγR expression (58) and stimulation of 12/15-lipoxygenase expression (59), this lectin favors macrophage conversion into a proresolving phenotype. In addition, Gal-1 stimulated monocyte chemotaxis (60), suggesting that this lectin endows macrophages with a combined proresolving and promigratory phenotype. Likewise, this lectin may impart a distinctive immunoregulatory program in DCs that is characterized by migratory and tolerogenic profiles. Exogenous and endogenous Gal-1 contribute to differentiation of tolerogenic DCs through mechanisms involving IL-27 and IL-10 (27). Accordingly, DCs lacking Gal-1 were consistently more immunogenic than wild-type (WT) DCs, favored polarization toward Th1 and Th17 profiles, and counteracted Treg responses (27, 37). In contrast, Gal-1 promoted DC migration and maturation (61, 62) and inhibited tissue emigration of immunogenic, but not tolerogenic, DCs through mechanisms involving differential core 2 *O*-glycosylation of CD43 (63). This selective effect provides an additional mechanism for the unique anti-inflammatory function of this lectin involving both tolerogenic and promigratory profiles.

Taming T cell and B cell functions: adaptive immune programs silenced by Gal-1

Mounting evidence highlights a major role for Gal-1–glycan interactions in shaping the profile of individual T cell subsets controlling their activation, differentiation, survival, and cytokine production (64). Functional assays identified Gal-1 as a novel CD69-binding partner that controls differentiation of Th17 cells (20). Moreover, Gal-1 has been shown to control T cell survival by interacting with different components of the cell death machinery. Through binding to *N*- and *O*-glycans

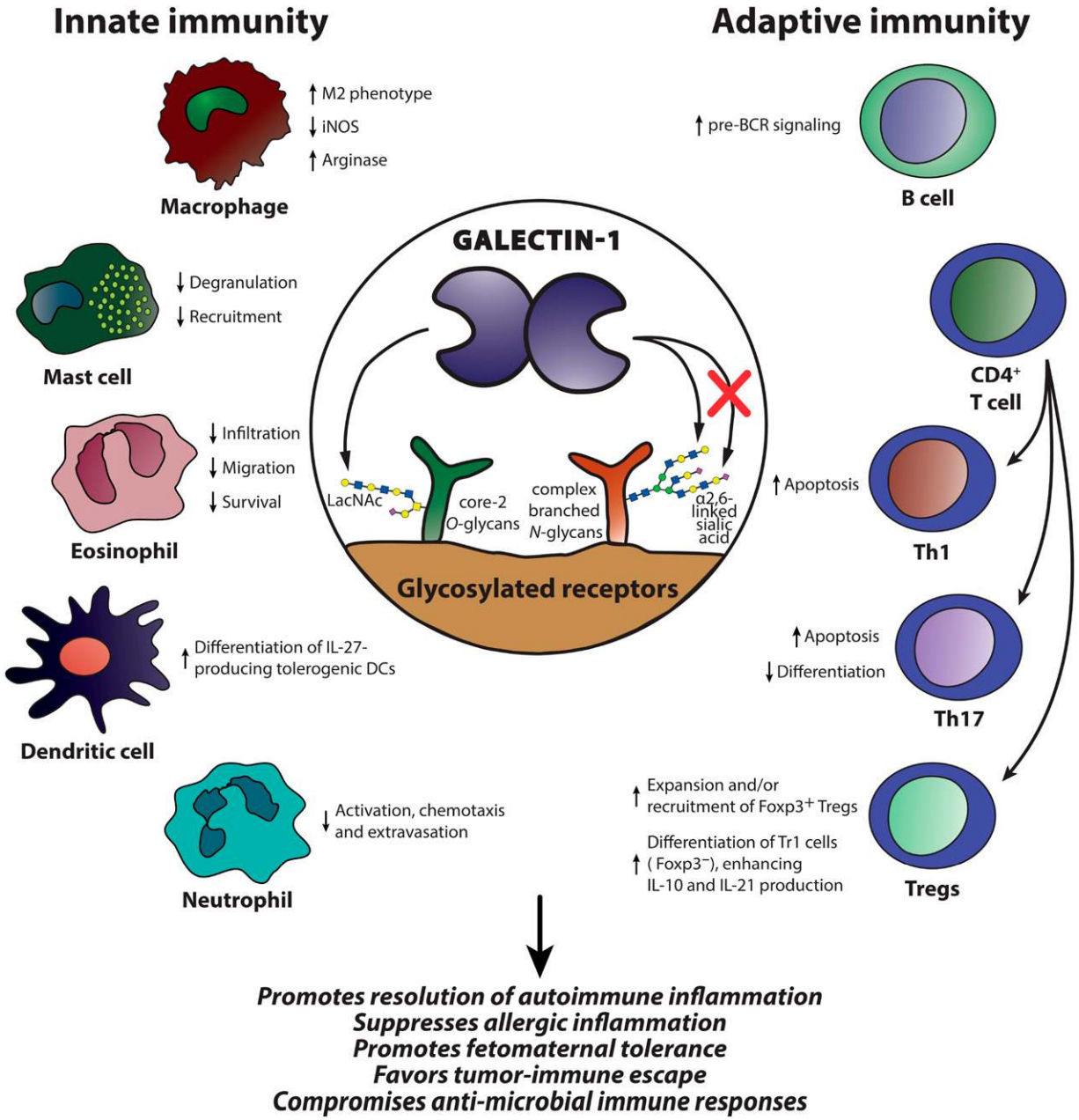

FIGURE 1. Regulatory programs mediated by Gal-1 in innate and adaptive immunity. A dynamic glycosylation signature on target cells controls the immunoregulatory activities of Gal-1: although poly-LacNAc branching on core-2 *O*-glycans and complex *N*-glycans is critical for Gal-1 binding, α2,6-linked sialic acid prevents Gal-1 function. By interacting with a variety of glycosylated receptors, this lectin translates glycan-containing information into regulatory programs that control immune cell homeostasis. Gal-1 promotes resolution of acute inflammation by modulating the fate and function of innate immune cells, including macrophages, DCs, mast cells, eosinophils, and neutrophils. In contrast, this lectin controls adaptive immune programs by modulating survival and differentiation of Th1 and Th17 lymphocytes and facilitating tolerogenic circuits mediated by DCs, Foxp3$^+$ Tregs, and Foxp3$^-$ regulatory T (Tr1) cells. In addition, Gal-1 shapes the B cell compartment by influencing pre-BCR signaling, and modulating transition toward plasma cell or memory B cell phenotypes. These glycan-dependent regulatory programs may promote the resolution of autoimmune and allergic inflammation, favor fetomaternal tolerance, facilitate tumor-immune escape, and compromise antimicrobial immune responses.

present in CD45, CD43, and CD7 (65), or by sensitizing T cells to the Fas-mediated pathway (66), exogenous Gal-1 has been shown to engage cell death programs. Moreover, recent studies showed that intracellular Gal-1 sensitizes T cells to apoptosis induced by extracellular Gal-1, an effect that was substantiated in cells from systemic lupus erythematosus patients, which express lower Gal-1 levels and are less sensitive to exogenous Gal-1 than T cells from healthy subjects (67). However, other studies showed that recombinant Gal-1 does not promote T cell death in the absence of DTT, a reducing agent used to avoid oxidation of this lectin (68). Notwithstanding, experiments aimed at exploring the relevance of endogenous Gal-1 in vivo revealed changes in T cell viability when this lectin was knocked down in tumor cells (42, 69) or when *Lgals1*$^{-/-}$ mice were challenged with inflammatory stimuli (70), suggesting direct or indirect roles for Gal-1 in controlling T cell fate. Using in vitro and in vivo approaches, we found that Gal-1 selectively controls the fate of fully activated Th1- and Th17-polarized cells, because these cells express the repertoire of glycans that are critical for Gal-1 binding, whereas Th2 cells are resistant to this lectin as a

result of increased α2,6-sialylation of cell surface glycoproteins (70). This mechanism may account for the enhanced frequency of Th1 and Th17 cells in Ag-challenged *Lgals1*$^{-/-}$ mice (70) and may explain Th2-skewed responses induced by Gal-1 in models of autoimmunity and cancer (71). Additionally, Gal-1 may impair T cell function by antagonizing TCR signals (72) and favoring IL-10 secretion (73–76), suggesting multiple pathways used by this lectin to control T cell responses.

In addition to its inhibitory roles in effector T cells, Gal-1 may shape the function of Tregs by supporting their differentiation, expansion, and immunosuppressive potential. In models of pregnancy, parasite infection, autoimmunity, and breast cancer, Gal-1 triggered the expansion and/or recruitment of Tregs (26, 31, 37, 76). Moreover, Foxp3^{+} Tregs (25) and regulatory γδ T cells (29) express high amounts of Gal-1, which contribute to the immunosuppressive function of these cells. Although the precise role of Gal-1 in Treg-induced immunosuppression is still poorly understood, Wang et al. (77) reported a possible mechanism by which Tregs inhibit effector T cells through a Gal-1–driven pathway involving the GM1 ganglioside and the TRPC5 channel. Future studies should be aimed at elucidating the biochemical nature and functional relevance of these interactions in vivo.

With regard to the B cell compartment, Gal-1 was identified as an essential component of the synapse established between stromal bone marrow cells and pre-B cells (78). Ligand-induced pre-BCR activation relied upon interactions among the pre-BCR, Gal-1, and $\alpha_4\beta_1$, $\alpha_5\beta_1$, and $\alpha_4\beta_7$ integrins, leading to pre-BCR clustering and signaling, with the consequent generation of pre-BII/stromal cell niches (79). Notably, the λ5 unique region of the pre-BCR represents an unusual example of a nonglycosylated extracellular protein partner of Gal-1, which docks onto a Gal-1 hydrophobic surface adjacent to its CRD and reduces Gal-1 affinity for LacNAc epitopes (21, 80). Within the mature B cell compartment, Gal-1 amplifies B cell activation by augmenting the strength of BCR signaling (81, 82). In the presence of Gal-1, suboptimal concentrations of anti-IgM triggered full BCR signals in leukemic B cells (81, 82), suggesting that Gal-1–glycan interactions act by decreasing the threshold for B cell activation. Moreover, Gal-1 controls transition of activated B cells toward memory B cell or plasma cell phenotypes (83, 84). Thus, Gal-1 exerts broad influence during the lifespan of immature and mature B cells by modulating immune synapses, signaling, and differentiation.

Gal-1 in autoimmune diseases: Resetting tolerogenic programs

Studies in different rodent models and human samples revealed critical roles for Gal-1 in the resolution of autoimmune inflammation (64).

Autoimmune CNS inflammation. By controlling the fate and signaling of T cells, DCs, and CNS immune populations, including microglia, astrocytes, and oligodendrocytes, Gal-1 influences the development, severity, and resolution of experimental autoimmune encephalomyelitis (EAE), a rodent model of multiple sclerosis (85). First reported in Lewis rats (86), Gal-1 reduced clinical signs of EAE through diverse mechanisms (85). Endogenous Gal-1 was selectively upregulated by tolerogenic stimuli, and its expression increased during the peak and resolution phases of EAE (27, 30). Interestingly, *Lgals1*$^{-/-}$ mice develop greater Th1 and Th17 responses, enhanced susceptibility to autoimmune neuroinflammation, and greater disease severity than their WT counterparts (70). At the mechanistic level, Gal-1 contributed to the resolution of EAE by selectively deleting Th1 and Th17 cells (70) or by inducing differentiation of tolerogenic DCs, which favor induction of IL-10–producing Tr1 cells through IL-27– and STAT3-dependent mechanisms (27). This immunoregulatory circuit also provided an explanatory mechanism for the underlying i.v. tolerance induced by MOG 35–55 administration (87).

Finally, in addition to its role within T cell and DC compartments, Gal-1 controls microglia polarization and function (30, 88, 89). We found that, in response to immunosuppressive stimuli, astrocytes may limit the activation of classically activated M1 microglia by secreting Gal-1, which hierarchically suppresses downstream proinflammatory mediators, such as inducible NO synthase, TNF, and CCL2, and tempers inflammation-induced neurodegeneration (30). Mice devoid of Gal-1 showed increased microglia activation, astrogliosis, demyelination, and axonal regeneration (30, 88).

Rheumatoid arthritis. Encouraged by its ability to impair T cell function and suppress proinflammatory cytokines (90, 91), the effects of Gal-1 were assessed in a collagen-induced arthritis model by gene and protein therapy strategies (92). Marked amelioration of the disease, enhanced susceptibility to Ag-induced T cell apoptosis, cytokine shift toward a Th2 response, and overall reduction of anti-collagen type II Ab were typical hallmarks of Gal-1–treated mice (92). Accordingly, Gal-1 expression decreased in synovial tissue from patients with juvenile idiopathic arthritis (93) and in joints of arthritic rats (94). These effects contrast with the broad proinflammatory and profibrotic activities of Gal-3 (94, 95), confirming different actions of individual members of the galectin family during the arthritogenic process. Moreover, lack of endogenous Gal-1 led to enhanced disease severity and a pronounced proinflammatory phenotype in *Lgals1*$^{-/-}$ arthritic mice (96).

Ocular inflammation. Studies in different models revealed a critical role for Gal-1 in the control of ocular inflammation. Systemic administration of recombinant Gal-1 early or late during the course of experimental autoimmune uveitis decreased leukocyte infiltration, as well as promoted a shift toward Th2 and Treg cytokine profiles, counteracting pathogenic Th1 cells and ameliorating ocular pathology (76). More recently, in a model of endotoxin-induced uveitis, Gal-1 treatment ameliorated clinical manifestations of the disease by decreasing leukocyte infiltration and release of proinflammatory cytokines (97). Likewise, Gal-1 suppressed *Pseudomonas aeruginosa*–induced corneal inflammation by reducing leukocyte infiltration, inhibiting proinflammatory responses, and favoring Th2- and IL-10–mediated anti-inflammatory programs (36). Interestingly, in a model of ocular immunopathology induced by HSV-1, Gal-1 reduced the severity of keratitis lesions and the extent of corneal vascularization (98).

Endogenous Gal-1 is abundantly expressed in different eye compartments, including cornea and retina (35, 99), and it mediates inhibition of T cell activation induced by retinal pigment epithelial cells (100), suggesting that it may prevent exuberant ocular inflammation. In this regard, increased frequency of neutralizing anti–Gal-1 Ab has been documented in sera from patients with autoimmune uveitis compared with healthy subjects (101). These findings, together with the potent immunosuppressive activity of this lectin, suggest a major role for the Gal-1–glycan axis in sustaining immune privilege and restraining ocular inflammation.

Testicular inflammation. Expression of Gal-1 is prominent in different cell types within the testis, including Sertoli cells and germ cells (33, 34, 102). In vitro, Gal-1 synthesized by Sertoli cells favored the differentiation of tolerogenic DCs (102), suggesting its potential role in creating an immunosuppressive testicular microenvironment. In contrast to other experimental models, *Lgals1*$^{-/-}$ mice showed reduced incidence and severity of experimental autoimmune orchitis compared with WT mice (34). However, administration of recombinant Gal-1 attenuated disease severity (34), suggesting different roles for endogenous versus exogenous Gal-1 in the regulation of testicular inflammation. Moreover, although a substantial increase in Gal-1 was reported during the peak of inflammation in other models (85), testis immunopathology was not associated with upregulation of this lectin (34). These results suggest context-dependent regulation of Gal-1 expression and function in the control of autoimmune inflammation.

Autoimmune diabetes. Given the ability of Gal-1 to target activated T cells, this lectin became a promising tool to treat type 1 diabetes (T1D) (103). In NOD mice, therapy with soluble Gal-1 prevented the onset of the disease (103). The preventive effect of Gal-1 on T1D was significantly associated with a reduction in Th1 immunity and increased frequency of IL-10– and IL-4–secreting CD4 T cells in response to pancreatic β cell Ag. In accordance with previous studies (92), this lectin induced apoptosis of pathogenic T cells (103).

In T1D, pancreatic β cell destruction results from activation of Ag-specific effector T cells evading the protective roles of Tregs (104). A primary defect in effector T cells that confers resistance to Treg suppression was suggested in NOD mice and subjects with T1D (104, 105). Notably, lack of GM1 expression by effector T cells preventing Gal-1 binding has been proposed as a potential mechanism of resistance to Treg-induced immunosuppression (77, 106). However, because Gal-1 binds to a variety of glycoconjugates (11), further studies are warranted to elucidate whether other galectin–receptor interactions might take place under these circumstances. Finally, in contrast to healthy pregnant women, patients with gestational diabetes mellitus did not show any significant changes in Gal-1 levels during gestation (46). Of note, an immune-endocrine circuit regulated during the resolution of T1D and gestational diabetes mellitus may govern the broad immunosuppressive activities of Gal-1, leading to Th2 cytokine polarization (70, 107) and Treg expansion (26, 31, 103).

Inflammatory bowel diseases. Inflammatory bowel diseases (IBDs) are chronic relapsing inflammatory disorders that affect the gastrointestinal tract. Crohn's disease and ulcerative colitis represent the two main forms of IBD, which differ in their anatomical, histological, and immunological features. Although Crohn's disease patients exhibit pronounced Th1 and Th17 responses, T cells from ulcerative colitis patients typically display a Th2 bias (108). Nevertheless, both pathologic conditions involve an aberrant activation of mucosal T cells against commensal microbiota, leading to inflammation and epithelial cell deregulation (109).

Several members of the galectin family, including Gal-1, -2, -3, and -4, play important roles in IBD (110–113). Treatment with Gal-1 resulted in improvement of clinical, histopathological, and immunological manifestations of intestinal inflammation in the 2,4,6-trinitrobenzenesulfonic acid–induced colitis model (39). In addition to normalization of mucosal architecture, administration of exogenous Gal-1 induced apoptosis of activated CD4$^+$ T cells in lamina propria and spleen and diminished the levels of proinflammatory cytokines in plasma and mucosal tissue (39). Interestingly, in human samples, Gal-1, -3, -4, and -9 were found to be homogeneously expressed throughout the colon, and their expression was higher in the colon than in the small intestine (114). Notably, unlike Gal-3, -4, and -9, Gal-1 expression was upregulated in inflamed versus noninflamed areas of IBD patients. Using a multivariate-linear discriminant analysis, a specific galectin signature could be identified that distinguished inflamed IBD from control tissue or from other intestinal inflammatory conditions (114). Inflammatory stimuli controlled Gal-1 binding to epithelial cells, influencing epithelial cell survival and production of tolerogenic cytokines (IL-10, IL-25, and TGF-β_1) (115, 116). Thus, either through elimination of Ag-experienced T cells or through modulation of inflammatory cytokines, Gal-1 promotes the resolution of gut inflammation, acting as a RAMP in mucosal homeostasis. These results integrate Gal-1 into the tolerogenic portfolio that coordinates the interplay between intestinal epithelial cells and the highly specialized gut immune system.

Gal-1 as a tuner of allergic inflammation and asthma

Allergic reactions occur clinically as anaphylaxis, urticaria, angioedema, rhinitis, atopic dermatitis, and asthma. A major breakthrough in understanding asthma pathogenesis was the recent characterization of different endotypes on the basis of distinct pathological mechanisms, such as Th2-high asthma and Th2-low asthma (117). Recent observations suggest that Gal-1 plays an important role in the control of airway infiltration by eosinophils. In a model of allergic asthma, allergen-challenged *Lgals1*$^{-/-}$mice showed an increased airway infiltration by eosinophils and T lymphocytes, as well as higher numbers of peripheral blood eosinophils, compared with WT mice (40). Consistent with these observations, *Lgals1*$^{-/-}$ mice showed more severe airway hyperresponsiveness associated with higher levels of TNF in the lung. Through inhibition of cell migration or induction of eosinophil apoptosis, Gal-1 reduced eosinophil recruitment to the airways (40). The ability of Gal-1 to inhibit cell migration may not be restricted to eosinophils, because this lectin also inhibits lymphocyte trafficking in vitro and in vivo (118). Supporting the role for Gal-1 in the pathogenesis of asthma, macrophages from sputum samples of asthma patients expressed lower Gal-1 levels than those isolated from healthy donors (119). Interestingly, corticosteroids, the first-line and most effective treatment for asthma, induced a pronounced increase in Gal-1 expression in human nasal polyps, suggesting that glucocorticoids' action in asthmatic patients could be partially mediated through an increased synthesis of Gal-1 in the airways (120, 121). In a murine model of oral allergy syndrome, administration of Gal-1 suppressed allergic reaction induced by food allergens by inhibiting IL-4 production, recruitment of mast cells and eosinophils, and synthesis of histamine (41). More recently, Gal-1 has been shown to synergize with allergen-specific immunotherapy, providing long-term benefits in animal models by targeting mast cells and facilitating Treg development (122). Overall, these reports suggest that

Gal-1 influences the resolution of allergic reactions and might represent a useful tool for the treatment of allergic diseases.

Gal-1 in pregnancy: the sweet privilege

Research over the past few years has identified essential roles for galectins, particularly Gal-1, in tolerance mechanisms that operate at the fetomaternal interface (123). Gal-1 is present in the female reproductive tract and is significantly upregulated during pregnancy (31, 32, 123, 124). In human placenta, Gal-1 is expressed by various cell types primarily regulated by progesterone and proinflammatory cytokines (32, 123).

In a model of stress-induced pregnancy failure (31), *Lgals1*$^{-/-}$ mice showed higher rates of fetal loss compared with their WT counterparts in allogeneic, but not syngeneic, matings. Administration of Gal-1 prevented fetal loss and restored tolerance in vivo (31). Accordingly, human uterine NK cells inhibited the viability of decidual T cells via glycosylation-dependent Gal-1–mediated mechanisms (125). Moreover, transcriptional activity of NF-κB was altered by Gal-1 in human decidual cells, limiting the production of IL-6 (126). Mechanistically, Gal-1 conferred immune privilege to human trophoblast cells by limiting T cell viability, dampening Th1-type cytokines, and favoring expansion of Tregs (32). In line with these findings, patients with recurrent pregnancy loss had considerably lower levels of circulating Gal-1 and a higher frequency of anti–Gal-1 autoantibodies compared with sera from fertile women (32). Finally, other studies suggested that Gal-1 contributes to immunoregulation, placentation, and fetal growth mediated by uterine mast cells (127). Altogether, these findings support a protective role for Gal-1 in immune tolerance at the fetomaternal interface.

Usurping the Gal-1 pathway to thwart antitumor immunity

Immunosuppressive pathways that promote resolution of inflammation may be co-opted by cancer cells or their adjoining microenvironment to thwart antitumor responses (128). Using mouse melanoma models and human patient samples, we identified an essential role for Gal-1 as a mediator of tumor-immune escape (42). This effect was confirmed by disruption of Gal-1 ligands in vivo following administration of a metabolic inhibitor of LacNAc biosynthesis, which restrained tumor progression by stimulating antitumor immunity (129). Further studies demonstrated that Gal-1 also confers immune privilege to classical Hodgkin lymphoma by favoring a non-productive immune infiltrate dominated by Th2 cells and Foxp3^{+} Tregs (130). Interestingly, in classical Hodgkin lymphoma and posttransplant lymphoproliferative disorders, two hematological malignancies associated with EBV infection, Gal-1 expression was driven by an enhancer of the AP-1 transcription factor (130, 131), suggesting that oncogenic viruses may usurp the Gal-1 pathway to promote immune escape. Likewise, Kaposi's sarcoma–associated herpes virus induced Gal-1 expression, which coupled angiogenesis, inflammation, and tumorigenesis in Kaposi's sarcoma (43). Remarkably, co-option of the Gal-1–glycan pathway as a major immune-evasive program was demonstrated in a number of tumor models, including lung, breast, pancreatic, and ovarian carcinoma, as well as glioblastoma, neuroblastoma, and T cell lymphoma (19, 26, 28, 29, 42–44, 69, 132–136). The mechanisms underlying these immune-inhibitory effects vary significantly among different tumor types and include expansion of Tregs, differentiation of tolerogenic DCs, induction of T cell apoptosis, promotion of a Th2 cytokine profile, deactivation of macrophages, T cell exclusion, and inhibition of NK cell function (4). Interestingly, reinvigoration of antitumor responses observed upon disruption of galectin-specific ligands (i.e., complex branched *N*-glycans) was even more impressive than that observed in response to Gal-1 blockade (19), suggesting the contribution of other members of the galectin family to tumor-driven immunosuppression. Accordingly, Gal-3 promotes T cell dysfunction by directly interacting with LAG-3 or by distancing the TCR from CD8 molecules (15, 137), whereas Gal-9 limited antitumor immunity by engaging Dectin-1 on tumor-associated macrophages (16).

Notably, although Gal-1 is typically upregulated in cancer cells, in some tumor types, immune or stromal cells appear to be the main Gal-1 source. Particularly in ovarian cancer models, γδ T lymphocytes and myeloid-derived suppressor cells emerge as major Gal-1 producers, linking TLR5-dependent inflammation, systemic immunosuppression, and tumor progression (29). Moreover, this lectin is preferentially expressed in a subset of Satb1-driven Zbtb46^{+} immunosuppressive DCs that infiltrate ovarian tumors (28). Furthermore, in human chronic lymphocytic leukemia, Gal-1 is mainly secreted by nurse-like myeloid cells and macrophages, facilitating establishment of appropriate tumorigenic niches (81). Finally, Gal-1 expression, driven by hypoxic microenvironments, has been established as a link between tumor angiogenesis and immunosuppression (43) and as a key determinant of sensitivity to different anticancer therapies, including those targeting vascular endothelial growth factor (19, 138) and CD20 (139). Thus, blockade of Gal-1 or disruption of its specific glycosylated ligands may contribute to reduce tumor progression by attenuating immunosuppression and counteracting aberrant angiogenesis.

Subverting antimicrobial responses by co-opting the Gal-1 pathway

Mechanisms that promote resolution of inflammation may hinder orchestration of antimicrobial responses, but they may also counteract pathogen-induced immunopathology. Moreover, microbes may co-opt inhibitory pathways to subvert host protective immunity (1). Recently we found that Gal-1–driven tolerogenic circuits can repress protective immunity during infection with *Yersinia enterocolitica*, an enteropathogenic bacterium, by targeting local immunity, including NO production, NF-κB activation, and TNF synthesis, as well as systemic Th1 and Th17 responses (38). Similarly, in a model of *Trypanosoma cruzi* infection, Gal-1 fueled the activation of immunoregulatory circuits that hindered antiparasite immunity, particularly those involving differentiation of tolerogenic DCs and Tregs (37). Moreover, in an in vitro model of *Trichomonas vaginalis* infection, Gal-1 inhibited recruitment of phagocytes by suppressing central chemokines, primarily IL-8, MIP-3α, and RANTES (140). Thus, targeting the Gal-1–glycan axis may contribute to reinforce host protective immunity by counteracting local and systemic immunosuppressive programs. However, as mentioned above, administration of Gal-1 ameliorated corneal immunopathology induced by *Pseudomonas aeruginosa* by suppressing Th17 responses (36). Finally, Gal-1, as well as other galectins, have been proposed to serve as pathogen-recognition receptors that

could positively or negatively regulate inflammatory responses by sensing glycans on the surface of pathogenic microbes (141). Thus, Gal-1 may play multifaceted roles during infection by subverting antimicrobial responses, orchestrating host immunity, or curbing pathogen-driven immunopathology.

Conclusions

Excessive inflammation is widely appreciated as a critical component in almost all diseases, including autoimmune, neurodegenerative, and metabolic diseases, as well as infection, asthma, and cancer (2). Gal-1 has emerged as a potent homeostatic signal that, together with other anti-inflammatory mediators and RAMPS, controls unresolved inflammation and limits immunopathology while hindering antimicrobial and antitumor responses. The mechanisms underlying these effects range from modulation of macrophage polarization, inhibition of eosinophil and neutrophil trafficking, induction of tolerogenic DCs, expansion of Tregs, and modulation of T cell function to control of cytokine synthesis (Fig. 1). These broad immunoregulatory activities open novel therapeutic opportunities for reprogramming innate and adaptive immunity in a wide range of inflammatory conditions. Although Gal-1–targeted therapies, using neutralizing anti–Gal-1 mAb, glycoamines, or synthetic peptides, have been designed and validated in preclinical models to reinforce antitumor and antimicrobial immunity, Gal-1–agonistic drugs for limiting unresolved inflammation in diverse inflammation conditions are anticipated to be released (6, 19, 43, 131, 142). However, before Gal-1–based therapeutic agents will be embraced, several questions remain to be addressed: Do other members of the galectin family play compensatory roles in response to Gal-1 blockade? Why does Gal-1 bind to a preferential set of glycosylated receptors even though glycan ligands are ubiquitously expressed in a wide range of receptors? Do protein–protein interactions play any role in Gal-1 receptor association that could be targeted as an alternative therapeutic approach? What is the therapeutic advantage of blocking individual galectins instead of targeting a set of galectins with similar or complementary regulatory activities? Thus, although evidence presented in this article supports the multiple regulatory functions of Gal-1, its possible mechanisms of action, and its broad therapeutic potential, progress made thus far might represent only the "tip of an iceberg" within the exciting field of glycoimmunology, with more mechanistic insights and therapeutic approaches awaiting future discovery.

Disclosures

The authors have no financial conflicts of interest.

References

1. Buckley, C. D., D. W. Gilroy, C. N. Serhan, B. Stockinger, and P. P. Tak. 2013. The resolution of inflammation. *Nat. Rev. Immunol.* 13: 59–66.
2. Serhan, C. N. 2014. Pro-resolving lipid mediators are leads for resolution physiology. *Nature* 510: 92–101.
3. Shields, A. M., G. S. Panayi, and V. M. Corrigall. 2011. Resolution-associated molecular patterns (RAMP): RAMParts defending immunological homeostasis? *Clin. Exp. Immunol.* 165: 292–300.
4. Méndez-Huergo, S. P., A. G. Blidner, and G. A. Rabinovich. 2017. Galectins: emerging regulatory checkpoints linking tumor immunity and angiogenesis. *Curr. Opin. Immunol.* 45: 8–15.
5. Sato, S., C. St-Pierre, P. Bhaumik, and J. Nieminen. 2009. Galectins in innate immunity: dual functions of host soluble beta-galactoside-binding lectins as damage-associated molecular patterns (DAMPs) and as receptors for pathogen-associated molecular patterns (PAMPs). *Immunol. Rev.* 230: 172–187.
6. Cerliani, J. P., A. G. Blidner, M. A. Toscano, D. O. Croci, and G. A. Rabinovich. 2017. Translating the 'sugar code' into immune and vascular signaling programs. *Trends Biochem. Sci.* 42: 255–273.
7. Liu, F. T., R. J. Patterson, and J. L. Wang. 2002. Intracellular functions of galectins. *Biochim. Biophys. Acta* 1572: 263–273.
8. Rabinovich, G. A., M. A. Toscano, S. S. Jackson, and G. R. Vasta. 2007. Functions of cell surface galectin-glycoprotein lattices. *Curr. Opin. Struct. Biol.* 17: 513–520.
9. Nickel, W. 2003. The mystery of nonclassical protein secretion. A current view on cargo proteins and potential export routes. *Eur. J. Biochem.* 270: 2109–2119.
10. Cho, M., and R. D. Cummings. 1995. Galectin-1, a beta-galactoside-binding lectin in Chinese hamster ovary cells. II. Localization and biosynthesis. *J. Biol. Chem.* 270: 5207–5212.
11. Thiemann, S., and L. G. Baum. 2016. Galectins and immune responses-Just how do they do those things they do? *Annu. Rev. Immunol.* 34: 243–264.
12. Hsu, D. K., R. Y. Yang, Z. Pan, L. Yu, D. R. Salomon, W. P. Fung-Leung, and F. T. Liu. 2000. Targeted disruption of the galectin-3 gene results in attenuated peritoneal inflammatory responses. *Am. J. Pathol.* 156: 1073–1083.
13. Steichen, A. L., T. J. Simonson, S. L. Salmon, D. W. Metzger, B. B. Mishra, and J. Sharma. 2015. Alarmin function of galectin-9 in murine respiratory tularemia. *PLoS One* 10: e0123573.
14. Yip, P. K., A. Carrillo-Jimenez, P. King, A. Vilalta, K. Nomura, C. C. Chau, A. M. Egerton, Z. H. Liu, A. J. Shetty, J. L. Tremoleda, et al. 2017. Galectin-3 released in response to traumatic brain injury acts as an alarmin orchestrating brain immune response and promoting neurodegeneration. *Sci. Rep.* 7: 41689.
15. Kouo, T., L. Huang, A. B. Pucsek, M. Cao, S. Solt, T. Armstrong, and E. Jaffee. 2015. Galectin-3 shapes antitumor immune responses by suppressing CD8+ T cells via LAG-3 and inhibiting expansion of plasmacytoid dendritic cells. *Cancer Immunol. Res.* 3: 412–423.
16. Daley, D., V. R. Mani, N. Mohan, N. Akkad, A. Ochi, D. W. Heindel, K. B. Lee, C. P. Zambirinis, G. S. B. Pandian, S. Savadkar, et al. 2017. Dectin 1 activation on macrophages by galectin 9 promotes pancreatic carcinoma and peritumoral immune tolerance. *Nat. Med.* 23: 556–567.
17. Di Lella, S., V. Sundblad, J. P. Cerliani, C. M. Guardia, D. A. Estrin, G. R. Vasta, and G. A. Rabinovich. 2011. When galectins recognize glycans: from biochemistry to physiology and back again. *Biochemistry* 50: 7842–7857.
18. Stowell, S. R., M. Cho, C. L. Feasley, C. M. Arthur, X. Song, J. K. Colucci, S. Karmakar, P. Mehta, M. Dias-Baruffi, R. P. McEver, and R. D. Cummings. 2009. Ligand reduces galectin-1 sensitivity to oxidative inactivation by enhancing dimer formation. *J. Biol. Chem.* 284: 4989–4999.
19. Croci, D. O., J. P. Cerliani, T. Dalotto-Moreno, S. P. Méndez-Huergo, I. D. Mascanfroni, S. Dergan-Dylon, M. A. Toscano, J. J. Caramelo, J. J. García-Vallejo, J. Ouyang, et al. 2014. Glycosylation-dependent lectin-receptor interactions preserve angiogenesis in anti-VEGF refractory tumors. *Cell* 156: 744–758.
20. de la Fuente, H., A. Cruz-Adalia, G. Martinez Del Hoyo, D. Cibrián-Vera, P. Bonay, D. Pérez-Hernández, J. Vázquez, P. Navarro, R. Gutierrez-Gallego, M. Ramirez-Huesca, et al. 2014. The leukocyte activation receptor CD69 controls T cell differentiation through its interaction with galectin-1. *Mol. Cell. Biol.* 34: 2479–2487.
21. Bonzi, J., O. Bornet, S. Betzi, B. T. Kasper, L. K. Mahal, S. J. Mancini, C. Schiff, C. Sebban-Kreuzer, F. Guerlesquin, and L. Elantak. 2015. Pre-B cell receptor binding to galectin-1 modifies galectin-1/carbohydrate affinity to modulate specific galectin-1/glycan lattice interactions. *Nat. Commun.* 6: 6194.
22. Fuertes, M. B., L. L. Molinero, M. A. Toscano, J. M. Ilarregui, N. Rubinstein, L. Fainboim, N. W. Zwirner, and G. A. Rabinovich. 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: 177–185.
23. Zuñiga, E., G. A. Rabinovich, M. M. Iglesias, and A. Gruppi. 2001. Regulated expression of galectin-1 during B-cell activation and implications for T-cell apoptosis. *J. Leukoc. Biol.* 70: 73–79.
24. Rabinovich, G., L. Castagna, C. Landa, C. M. Riera, and C. Sotomayor. 1996. Regulated expression of a 16-kd galectin-like protein in activated rat macrophages. *J. Leukoc. Biol.* 59: 363–370.
25. Garín, M. I., C. C. Chu, D. Golshayan, E. Cernuda-Morollón, R. Wait, and R. I. Lechler. 2007. Galectin-1: a key effector of regulation mediated by CD4+CD25+ T cells. *Blood* 109: 2058–2065.
26. Dalotto-Moreno, T., D. O. Croci, J. P. Cerliani, V. C. Martinez-Allo, S. Dergan-Dylon, S. P. Méndez-Huergo, J. C. Stupirski, D. Mazal, E. Osinaga, M. A. Toscano, et al. 2013. Targeting galectin-1 overcomes breast cancer-associated immunosuppression and prevents metastatic disease. *Cancer Res.* 73: 1107–1117.
27. Ilarregui, J. M., D. O. Croci, G. A. Bianco, M. A. Toscano, M. Salatino, M. E. Vermeulen, J. R. Geffner, and G. A. Rabinovich. 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: 981–991.
28. Tesone, A. J., M. R. Rutkowski, E. Brencicova, N. Svoronos, A. Perales-Puchalt, T. L. Stephen, M. J. Allegrezza, K. K. Payne, J. M. Nguyen, J. Wickramasinghe, et al. 2016. Satb1 overexpression drives tumor-promoting activities in cancer-associated dendritic cells. *Cell Reports* 14: 1774–1786.
29. Rutkowski, M. R., T. L. Stephen, N. Svoronos, M. J. Allegrezza, A. J. Tesone, A. Perales-Puchalt, E. Brencicova, X. Escovar-Fadul, J. M. Nguyen, M. G. Cadungog, et al. 2015. Microbially driven TLR5-dependent signaling governs distal malignant progression through tumor-promoting inflammation. *Cancer Cell* 27: 27–40.
30. Starossom, S. C., I. D. Mascanfroni, J. Imitola, L. Cao, K. Raddassi, S. F. Hernandez, R. Bassil, D. O. Croci, J. P. Cerliani, D. Delacour, et al. 2012. Galectin-1 deactivates classically activated microglia and protects from inflammation-induced neurodegeneration. *Immunity* 37: 249–263.

31. Blois, S. M., J. M. Ilarregui, M. Tometten, M. Garcia, A. S. Orsal, R. Cordo-Russo, M. A. Toscano, G. A. Bianco, P. Kobelt, B. Handjiski, et al. 2007. A pivotal role for galectin-1 in fetomaternal tolerance. *Nat. Med.* 13: 1450–1457.
32. Ramhorst, R. E., L. Giribaldi, L. Fraccaroli, M. A. Toscano, J. C. Stupirski, M. D. Romero, E. S. Durand, N. Rubinstein, A. Blaschitz, P. Sedlmayr, et al. 2012. Galectin-1 confers immune privilege to human trophoblast: implications in recurrent fetal loss. *Glycobiology* 22: 1374–1386.
33. Dettin, L., N. Rubinstein, A. Aoki, G. A. Rabinovich, and C. A. Maldonado. 2003. Regulated expression and ultrastructural localization of galectin-1, a pro-apoptotic beta-galactoside-binding lectin, during spermatogenesis in rat testis. *Biol. Reprod.* 68: 51–59.
34. Pérez, C. V., L. G. Gómez, G. S. Gualdoni, L. Lustig, G. A. Rabinovich, and V. A. Guazzone. 2015. Dual roles of endogenous and exogenous galectin-1 in the control of testicular immunopathology. *Sci. Rep.* 5: 12259.
35. Ridano, M. E., P. V. Subirada, M. C. Paz, V. E. Lorenc, J. C. Stupirski, A. L. Gramajo, J. D. Luna, D. O. Croci, G. A. Rabinovich, and M. C. Sánchez. 2017. Galectin-1 expression imprints a neurovascular phenotype in proliferative retinopathies and delineates responses to anti-VEGF. *Oncotarget* 8: 32505–32522
36. Suryawanshi, A., Z. Cao, T. Thitiprasert, T. S. Zaidi, and N. Panjwani. 2013. Galectin-1–mediated suppression of *Pseudomonas aeruginosa*–induced corneal immunopathology. *J. Immunol.* 190: 6397–6409.
37. Poncini, C. V., J. M. Ilarregui, E. I. Batalla, S. Engels, J. P. Cerliani, M. A. Cucher, Y. van Kooyk, S. M. González-Cappa, and G. A. Rabinovich. 2015. *Trypanosoma cruzi* infection imparts a regulatory program in dendritic cells and T cells via galectin-1–dependent mechanisms. *J. Immunol.* 195: 3311–3324.
38. Davicino, R. C., S. P. Méndez-Huergo, R. J. Eliçabe, J. C. Stupirski, I. Autenrieth, M. S. Di Genaro, and G. A. Rabinovich. 2017. Galectin-1–driven tolerogenic programs aggravate *Yersinia enterocolitica* infection by repressing antibacterial immunity. *J. Immunol.* 199: 1382–1392.
39. Santucci, L., S. Fiorucci, N. Rubinstein, A. Mencarelli, B. Palazzetti, B. Federici, G. A. Rabinovich, and A. Morelli. 2003. Galectin-1 suppresses experimental colitis in mice. *Gastroenterology* 124: 1381–1394.
40. Ge, X. N., S. G. Ha, Y. G. Greenberg, A. Rao, I. Bastan, A. G. Blidner, S. P. Rao, G. A. Rabinovich, and P. Sriramarao. 2016. Regulation of eosinophilia and allergic airway inflammation by the glycan-binding protein galectin-1. *Proc. Natl. Acad. Sci. USA* 113: E4837–E4846.
41. Xie, R. D., L. Z. Xu, L. T. Yang, S. Wang, Q. Liu, Z. G. Liu, and P. C. Yang. 2017. Galectin-1 inhibits oral-intestinal allergy syndrome. *Oncotarget* 8: 13214–13222.
42. Rubinstein, N., M. Alvarez, N. W. Zwirner, M. A. Toscano, J. M. Ilarregui, A. Bravo, J. Mordoh, L. Fainboim, O. L. Podhajcer, and G. A. Rabinovich. 2004. 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* 5: 241–251.
43. Croci, D. O., M. Salatino, N. Rubinstein, J. P. Cerliani, L. E. Cavallin, H. J. Leung, J. Ouyang, J. M. Ilarregui, M. A. Toscano, C. I. Domaica, et al. 2012. Disrupting galectin-1 interactions with N-glycans suppresses hypoxia-driven angiogenesis and tumorigenesis in Kaposi's sarcoma. *J. Exp. Med.* 209: 1985–2000.
44. Martínez-Bosch, N., M. G. Fernández-Barrena, M. Moreno, E. Ortiz-Zapater, J. Munné-Collado, M. Iglesias, S. André, H. J. Gabius, R. F. Hwang, F. Poirier, et al. 2014. Galectin-1 drives pancreatic carcinogenesis through stroma remodeling and Hedgehog signaling activation. *Cancer Res.* 74: 3512–3524.
45. Bastón, J. I., R. I. Barañao, A. G. Ricci, M. A. Bilotas, C. N. Olivares, J. J. Singla, A. M. Gonzalez, J. C. Stupirski, D. O. Croci, G. A. Rabinovich, and G. F. Meresman. 2014. Targeting galectin-1–induced angiogenesis mitigates the severity of endometriosis. *J. Pathol.* 234: 329–337.
46. Blois, S. M., B. Y. Gueuvoghlanian-Silva, I. Tirado-González, M. R. Torloni, N. Freitag, R. Mattar, M. L. Conrad, L. Unverdorben, G. Barrientos, J. Knabl, et al. 2014. Getting too sweet: galectin-1 dysregulation in gestational diabetes mellitus. *Mol. Hum. Reprod.* 20: 644–649.
47. Seropian, I. M., J. P. Cerliani, S. Toldo, B. W. Van Tassell, J. M. Ilarregui, G. E. González, M. Matoso, F. N. Salloum, R. Melchior, R. J. Gelpi, et al. 2013. Galectin-1 controls cardiac inflammation and ventricular remodeling during acute myocardial infarction. *Am. J. Pathol.* 182: 29–40.
48. Medzhitov, R. 2008. Origin and physiological roles of inflammation. *Nature* 454: 428–435.
49. Nathan, C., and A. Ding. 2010. Nonresolving inflammation. *Cell* 140: 871–882.
50. Rabinovich, G. A., C. E. Sotomayor, C. M. Riera, I. Bianco, and S. G. Correa. 2000. Evidence of a role for galectin-1 in acute inflammation. *Eur. J. Immunol.* 30: 1331–1339.
51. La, M., T. V. Cao, G. Cerchiaro, K. Chilton, J. Hirabayashi, K. Kasai, S. M. Oliani, Y. Chernajovsky, and M. Perretti. 2003. A novel biological activity for galectin-1: inhibition of leukocyte-endothelial cell interactions in experimental inflammation. *Am. J. Pathol.* 163: 1505–1515.
52. Cooper, D., L. V. Norling, and M. Perretti. 2008. Novel insights into the inhibitory effects of galectin-1 on neutrophil recruitment under flow. *J. Leukoc. Biol.* 83: 1459–1466.
53. Iqbal, A. J., A. L. Sampaio, F. Maione, K. V. Greco, T. Niki, M. Hirashima, M. Perretti, and D. Cooper. 2011. Endogenous galectin-1 and acute inflammation: emerging notion of a galectin-9 pro-resolving effect. *Am. J. Pathol.* 178: 1201–1209.
54. Stowell, S. R., S. Karmakar, C. M. Arthur, T. Ju, L. C. Rodrigues, T. B. Riul, M. Dias-Baruffi, J. Miner, R. P. McEver, and R. D. Cummings. 2009. Galectin-1 induces reversible phosphatidylserine exposure at the plasma membrane. *Mol. Biol. Cell* 20: 1408–1418.
55. Auvynet, C., S. Moreno, E. Melchy, I. Coronado-Martínez, J. L. Montiel, I. Aguilar-Delfin, and Y. Rosenstein. 2013. Galectin-1 promotes human neutrophil migration. *Glycobiology* 23: 32–42.
56. Correa, S. G., C. E. Sotomayor, M. P. Aoki, C. A. Maldonado, and G. A. Rabinovich. 2003. Opposite effects of galectin-1 on alternative metabolic pathways of L-arginine in resident, inflammatory, and activated macrophages. *Glycobiology* 13: 119–128.
57. Zúñiga, E., A. Gruppi, J. Hirabayashi, K. I. Kasai, and G. A. Rabinovich. 2001. Regulated expression and effect of galectin-1 on *Trypanosoma cruzi*–infected macrophages: modulation of microbicidal activity and survival. *Infect. Immun.* 69: 6804–6812.
58. Barrionuevo, P., M. Beigier-Bompadre, J. M. Ilarregui, M. A. Toscano, G. A. Bianco, M. A. Isturiz, and G. A. Rabinovich. 2007. A novel function for galectin-1 at the crossroad of innate and adaptive immunity: galectin-1 regulates monocyte/macrophage physiology through a nonapoptotic ERK-dependent pathway. *J. Immunol.* 178: 436–445.
59. Rostoker, R., H. Yaseen, S. Schif-Zuck, R. G. Lichtenstein, G. A. Rabinovich, and A. Ariel. 2013. Galectin-1 induces 12/15-lipoxygenase expression in murine macrophages and favors their conversion toward a pro-resolving phenotype. *Prostaglandins Other Lipid Mediat.* 107: 85–94.
60. Malik, R. K., R. R. Ghurye, D. J. Lawrence-Watt, and H. J. Stewart. 2009. Galectin-1 stimulates monocyte chemotaxis via the p44/42 MAP kinase pathway and a pertussis toxin-sensitive pathway. *Glycobiology* 19: 1402–1407.
61. Fulcher, J. A., S. T. Hashimi, E. L. Levroney, M. Pang, K. B. Gurney, L. G. Baum, and B. Lee. 2006. Galectin-1–matured human monocyte-derived dendritic cells have enhanced migration through extracellular matrix. *J. Immunol.* 177: 216–226.
62. Fulcher, J. A., M. H. Chang, S. Wang, T. Almazan, S. T. Hashimi, A. U. Eriksson, X. Wen, M. Pang, L. G. Baum, R. R. Singh, and B. Lee. 2009. Galectin-1 co-clusters CD43/CD45 on dendritic cells and induces cell activation and migration through Syk and protein kinase C signaling. *J. Biol. Chem.* 284: 26860–26870.
63. Thiemann, S., J. H. Man, M. H. Chang, B. Lee, and L. G. Baum. 2015. Galectin-1 regulates tissue exit of specific dendritic cell populations. *J. Biol. Chem.* 290: 22662–22677.
64. Rabinovich, G. A., and J. M. Ilarregui. 2009. Conveying glycan information into T-cell homeostatic programs: a challenging role for galectin-1 in inflammatory and tumor microenvironments. *Immunol. Rev.* 230: 144–159.
65. Stillman, B. N., D. K. Hsu, M. Pang, C. F. Brewer, P. Johnson, F. T. Liu, and L. G. Baum. 2006. Galectin-3 and galectin-1 bind distinct cell surface glycoprotein receptors to induce T cell death. *J. Immunol.* 176: 778–789.
66. Matarrese, P., A. Tinari, E. Mormone, G. A. Bianco, M. A. Toscano, B. Ascione, G. A. Rabinovich, and W. Malorni. 2005. Galectin-1 sensitizes resting human T lymphocytes to Fas (CD95)-mediated cell death via mitochondrial hyperpolarization, budding, and fission. *J. Biol. Chem.* 280: 6969–6985.
67. Deák, M., Á. Hornung, J. Novák, D. Demydenko, E. Szabó, Á. Czibula, R. Fajka-Boja, É. Kriston-Pál, É. Monostori, and L. Kovács. 2015. Novel role for galectin-1 in T-cells under physiological and pathological conditions. *Immunobiology* 220: 483–489.
68. Stowell, S. R., S. Karmakar, C. J. Stowell, M. Dias-Baruffi, R. P. McEver, and R. D. Cummings. 2007. Human galectin-1, -2, and -4 induce surface exposure of phosphatidylserine in activated human neutrophils but not in activated T cells. *Blood* 109: 219–227.
69. Banh, A., J. Zhang, H. Cao, D. M. Bouley, S. Kwok, C. Kong, A. J. Giaccia, A. C. Koong, and Q. T. Le. 2011. Tumor galectin-1 mediates tumor growth and metastasis through regulation of T-cell apoptosis. *Cancer Res.* 71: 4423–4431.
70. Toscano, M. A., G. A. Bianco, J. M. Ilarregui, D. O. Croci, J. Correale, J. D. Hernandez, N. W. Zwirner, F. Poirier, E. M. Riley, L. G. Baum, and G. A. Rabinovich. 2007. Differential glycosylation of TH1, TH2 and TH-17 effector cells selectively regulates susceptibility to cell death. *Nat. Immunol.* 8: 825–834.
71. Salatino, M., D. O. Croci, G. A. Bianco, J. M. Ilarregui, M. A. Toscano, and G. A. Rabinovich. 2008. Galectin-1 as a potential therapeutic target in autoimmune disorders and cancer. *Expert Opin. Biol. Ther.* 8: 45–57.
72. Liu, S. D., T. Tomassian, K. W. Bruhn, J. F. Miller, F. Poirier, and M. C. Miceli. 2009. Galectin-1 tunes TCR binding and signal transduction to regulate CD8 burst size. *J. Immunol.* 182: 5283–5295.
73. van der Leij, J., A. van den Berg, T. Blokzijl, G. Harms, H. van Goor, P. Zwiers, R. van Weeghel, S. Poppema, and L. Visser. 2004. Dimeric galectin-1 induces IL-10 production in T-lymphocytes: an important tool in the regulation of the immune response. *J. Pathol.* 204: 511–518.
74. Stowell, S. R., Y. Qian, S. Karmakar, N. S. Koyama, M. Dias-Baruffi, H. Leffler, R. P. McEver, and R. D. Cummings. 2008. Differential roles of galectin-1 and galectin-3 in regulating leukocyte viability and cytokine secretion. *J. Immunol.* 180: 3091–3102.
75. Cedeno-Laurent, F., M. Opperman, S. R. Barthel, V. K. Kuchroo, and C. J. Dimitroff. 2012. Galectin-1 triggers an immunoregulatory signature in Th cells functionally defined by IL-10 expression. *J. Immunol.* 188: 3127–3137.
76. Toscano, M. A., A. G. Commodaro, J. M. Ilarregui, G. A. Bianco, A. Liberman, H. M. Serra, J. Hirabayashi, L. V. Rizzo, and G. A. Rabinovich. 2006. Galectin-1 suppresses autoimmune retinal disease by promoting concomitant Th2- and T regulatory-mediated anti-inflammatory responses. *J. Immunol.* 176: 6323–6332.
77. Wang, J., Z. H. Lu, H. J. Gabius, C. Rohowsky-Kochan, R. W. Ledeen, and G. Wu. 2009. Cross-linking of GM1 ganglioside by galectin-1 mediates regulatory T cell activity involving TRPC5 channel activation: possible role in suppressing experimental autoimmune encephalomyelitis. *J. Immunol.* 182: 4036–4045.
78. Gauthier, L., B. Rossi, F. Roux, E. Termine, and C. Schiff. 2002. Galectin-1 is a stromal cell ligand of the pre-B cell receptor (BCR) implicated in synapse formation between pre-B and stromal cells and in pre-BCR triggering. *Proc. Natl. Acad. Sci. USA* 99: 13014–13019.
79. Espeli, M., S. J. Mancini, C. Breton, F. Poirier, and C. Schiff. 2009. Impaired B-cell development at the pre-BII-cell stage in galectin-1–deficient mice due to inefficient pre-BII/stromal cell interactions. *Blood* 113: 5878–5886.

80. Elantak, L., M. Espeli, A. Boned, O. Bornet, J. Bonzi, L. Gauthier, M. Feracci, P. Roche, F. Guerlesquin, and C. Schiff. 2012. Structural basis for galectin-1–dependent pre-B cell receptor (pre-BCR) activation. *J. Biol. Chem.* 287: 44703–44713.
81. Croci, D. O., P. E. Morande, S. Dergan-Dylon, M. Borge, M. A. Toscano, J. C. Stupirski, R. F. Bezares, J. S. Avalos, M. Narbaitz, R. Gamberale, et al. 2013. Nurse-like cells control the activity of chronic lymphocytic leukemia B cells via galectin-1. *Leukemia* 27: 1413–1416.
82. Tsai, C. M., H. Y. Wu, T. H. Su, C. W. Kuo, H. W. Huang, C. H. Chung, C. S. Chen, K. H. Khoo, Y. J. Chen, and K. I. Lin. 2014. Phosphoproteomic analyses reveal that galectin-1 augments the dynamics of B-cell receptor signaling. *J. Proteomics* 103: 241–253.
83. Tabrizi, S. J., H. Niiro, M. Masui, G. Yoshimoto, T. Iino, Y. Kikushige, T. Wakasaki, E. Baba, S. Shimoda, T. Miyamoto, et al. 2009. T cell leukemia/lymphoma 1 and galectin-1 regulate survival/cell death pathways in human naive and IgM+ memory B cells through altering balances in Bcl-2 family proteins. *J. Immunol.* 182: 1490–1499.
84. Anginot, A., M. Espeli, L. Chasson, S. J. Mancini, and C. Schiff. 2013. Galectin 1 modulates plasma cell homeostasis and regulates the humoral immune response. *J. Immunol.* 190: 5526–5533.
85. Mendez-Huergo, S. P., S. M. Maller, M. F. Farez, K. Mariño, J. Correale, and G. A. Rabinovich. 2014. Integration of lectin-glycan recognition systems and immune cell networks in CNS inflammation. *Cytokine Growth Factor Rev.* 25: 247–255.
86. Offner, H., B. Celnik, T. S. Bringman, D. Casentini-Borocz, G. E. Nedwin, and A. A. Vandenbark. 1990. Recombinant human beta-galactoside binding lectin suppresses clinical and histological signs of experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* 28: 177–184.
87. Mari, E. R., J. Rasouli, B. Ciric, J. N. Moore, J. R. Conejo-Garcia, N. Rajasagi, G. X. Zhang, G. A. Rabinovich, and A. Rostami. 2016. Galectin-1 is essential for the induction of MOG35-55–based intravenous tolerance in experimental autoimmune encephalomyelitis. *Eur. J. Immunol.* 46: 1783–1796.
88. Rinaldi, M., L. Thomas, P. Mathieu, P. Carabias, M. F. Troncoso, J. M. Pasquini, G. A. Rabinovich, and L. A. Pasquini. 2016. Galectin-1 circumvents lysolecithin-induced demyelination through the modulation of microglial polarization/phagocytosis and oligodendroglial differentiation. *Neurobiol. Dis.* 96: 127–143.
89. Aalinkeel, R., C. S. Mangum, E. Abou-Jaoude, J. L. Reynolds, M. Liu, K. Sundquist, N. U. Parikh, L. D. Chaves, M. J. Mammen, S. A. Schwartz, and S. D. Mahajan. 2017. Galectin-1 reduces neuroinflammation via modulation of nitric oxide-arginase signaling in HIV-1–transfected microglia: a gold nanoparticle–galectin-1 "Nanoplex" a possible neurotherapeutic? *J. Neuroimmune Pharmacol.* 12: 133–151.
90. Rabinovich, G. A., M. M. Iglesias, N. M. Modesti, L. F. Castagna, C. Wolfenstein-Todel, C. M. Riera, and C. E. Sotomayor. 1998. Activated rat macrophages produce a galectin-1–like protein that induces apoptosis of T cells: biochemical and functional characterization. *J. Immunol.* 160: 4831–4840.
91. Rabinovich, G. A., A. Ariel, R. Hershkoviz, J. Hirabayashi, K. I. Kasai, and O. Lider. 1999. Specific inhibition of T-cell adhesion to extracellular matrix and proinflammatory cytokine secretion by human recombinant galectin-1. *Immunology* 97: 100–106.
92. Rabinovich, G. A., G. Daly, H. Dreja, H. Tailor, C. M. Riera, J. Hirabayashi, and Y. Chernajovsky. 1999. Recombinant galectin-1 and its genetic delivery suppress collagen-induced arthritis via T cell apoptosis. *J. Exp. Med.* 190: 385–398.
93. Harjacek, M., S. Diaz-Cano, M. De Miguel, H. Wolfe, C. A. Maldonado, and G. A. Rabinovich. 2001. Expression of galectins-1 and -3 correlates with defective mononuclear cell apoptosis in patients with juvenile idiopathic arthritis. *J. Rheumatol.* 28: 1914–1922.
94. Wang, C. R., A. L. Shiau, S. Y. Chen, Z. S. Cheng, Y. T. Li, C. H. Lee, Y. T. Yo, C. W. Lo, Y. S. Lin, H. Y. Juan, et al. 2010. Intra-articular lentivirus-mediated delivery of galectin-3 shRNA and galectin-1 gene ameliorates collagen-induced arthritis. *Gene Ther.* 17: 1225–1233.
95. Filer, A., M. Bik, G. N. Parsonage, J. Fitton, E. Trebilcock, K. Howlett, M. Cook, K. Raza, D. L. Simmons, A. M. Thomas, et al. 2009. Galectin 3 induces a distinctive pattern of cytokine and chemokine production in rheumatoid synovial fibroblasts via selective signaling pathways. *Arthritis Rheum.* 60: 1604–1614.
96. Iqbal, A. J., D. Cooper, A. Vugler, B. R. Gittens, A. Moore, and M. Perretti. 2013. Endogenous galectin-1 exerts tonic inhibition on experimental arthritis. *J. Immunol.* 191: 171–177.
97. Zanon, Cde. F., N. M. Sonehara, A. P. Girol, C. D. Gil, and S. M. Oliani. 2015. Protective effects of the galectin-1 protein on in vivo and in vitro models of ocular inflammation. *Mol. Vis.* 21: 1036–1050
98. Rajasagi, N. K., A. Suryawanshi, S. Sehrawat, P. B. Reddy, S. Mulik, M. Hirashima, and B. T. Rouse. 2012. Galectin-1 reduces the severity of herpes simplex virus-induced ocular immunopathological lesions. *J. Immunol.* 188: 4631–4643.
99. Maldonado, C. A., L. F. Castagna, G. A. Rabinovich, and C. A. Landa. 1999. Immunocytochemical study of the distribution of a 16-kDa galectin in the chicken retina. *Invest. Ophthalmol. Vis. Sci.* 40: 2971–2977
100. Ishida, K., N. Panjwani, Z. Cao, and J. W. Streilein. 2003. Participation of pigment epithelium in ocular immune privilege. 3. Epithelia cultured from iris, ciliary body, and retina suppress T-cell activation by partially non-overlapping mechanisms. *Ocul. Immunol. Inflamm.* 11: 91–105.
101. Romero, M. D., J. C. Muiño, G. A. Bianco, M. Ferrero, C. P. Juarez, J. D. Luna, and G. A. Rabinovich. 2006. Circulating anti-galectin-1 antibodies are associated with the severity of ocular disease in autoimmune and infectious uveitis. *Invest. Ophthalmol. Vis. Sci.* 47: 1550–1556.
102. Gao, J., X. Wang, Y. Wang, F. Han, W. Cai, B. Zhao, Y. Li, S. Han, X. Wu, and D. Hu. 2016. Murine Sertoli cells promote the development of tolerogenic dendritic cells: a pivotal role of galectin-1. *Immunology* 148: 253–265.
103. Perone, M. J., S. Bertera, W. J. Shufesky, S. J. Divito, A. Montecalvo, A. R. Mathers, A. T. Larregina, M. Pang, N. Seth, K. W. Wucherpfennig, et al. 2009. Suppression of autoimmune diabetes by soluble galectin-1. *J. Immunol.* 182: 2641–2653.
104. D'Alise, A. M., V. Auyeung, M. Feuerer, J. Nishio, J. Fontenot, C. Benoist, and D. Mathis. 2008. The defect in T-cell regulation in NOD mice is an effect on the T-cell effectors. *Proc. Natl. Acad. Sci. USA* 105: 19857–19862.
105. Schneider, A., M. Rieck, S. Sanda, C. Pihoker, C. Greenbaum, and J. H. Buckner. 2008. The effector T cells of diabetic subjects are resistant to regulation via CD4+ FOXP3+ regulatory T cells. *J. Immunol.* 181: 7350–7355.
106. Wu, G., Z. H. Lu, H. J. Gabius, R. W. Ledeen, and D. Bleich. 2011. Ganglioside GM1 deficiency in effector T cells from NOD mice induces resistance to regulatory T-cell suppression. *Diabetes* 60: 2341–2349.
107. Motran, C. C., K. M. Molinder, S. D. Liu, F. Poirier, and M. C. Miceli. 2008. Galectin-1 functions as a Th2 cytokine that selectively induces Th1 apoptosis and promotes Th2 function. *Eur. J. Immunol.* 38: 3015–3027.
108. Neurath, M. F. 2014. Cytokines in inflammatory bowel disease. *Nat. Rev. Immunol.* 14: 329–342.
109. Nalle, S. C., and J. R. Turner. 2015. Intestinal barrier loss as a critical pathogenic link between inflammatory bowel disease and graft-versus-host disease. *Mucosal Immunol.* 8: 720–730.
110. Müller, S., T. Schaffer, B. Flogerzi, A. Fleetwood, R. Weimann, A. M. Schoepfer, and F. Seibold. 2006. Galectin-3 modulates T cell activity and is reduced in the inflamed intestinal epithelium in IBD. *Inflamm. Bowel Dis.* 12: 588–597.
111. Paclik, D., U. Berndt, C. Guzy, A. Dankof, S. Danese, P. Holzloehner, S. Rosewicz, B. Wiedenmann, B. M. Wittig, A. U. Dignass, and A. Sturm. 2008. Galectin-2 induces apoptosis of lamina propria T lymphocytes and ameliorates acute and chronic experimental colitis in mice. *J. Mol. Med. (Berl.)* 86: 1395–1406.
112. Paclik, D., S. Danese, U. Berndt, B. Wiedenmann, A. Dignass, and A. Sturm. 2008. Galectin-4 controls intestinal inflammation by selective regulation of peripheral and mucosal T cell apoptosis and cell cycle. *PLoS One* 3: e2629.
113. Nishida, A., K. Nagahama, H. Imaeda, A. Ogawa, C. W. Lau, T. Kobayashi, T. Hisamatsu, F. I. Preffer, E. Mizoguchi, H. Ikeuchi, et al. 2012. Inducible colitis-associated glycome capable of stimulating the proliferation of memory CD4+ T cells. *J. Exp. Med.* 209: 2383–2394.
114. Papa Gobbi, R., N. De Francesco, C. Bondar, C. Muglia, F. Chirdo, M. Rumbo, A. Rocca, M. A. Toscano, A. Sambuelli, G. A. Rabinovich, and G. H. Docena. 2016. A galectin-specific signature in the gut delineates Crohn's disease and ulcerative colitis from other human inflammatory intestinal disorders. *Biofactors* 42: 93–105
115. Muglia, C., N. Mercer, M. A. Toscano, M. Schattner, R. Pozner, J. P. Cerliani, R. P. Gobbi, G. A. Rabinovich, and G. H. Docena. 2011. The glycan-binding protein galectin-1 controls survival of epithelial cells along the crypt-villus axis of small intestine. *Cell Death Dis.* 2: e163.
116. Muglia, C. I., R. P. Gobbi, P. Smaldini, M. L. Delgado, M. Candia, C. Zanuzzi, A. Sambuelli, A. Rocca, M. A. Toscano, G. A. Rabinovich, and G. H. Docena. 2016. Inflammation controls sensitivity of human and mouse intestinal epithelial cells to galectin-1. *J. Cell. Physiol.* 231: 1575–1585.
117. Robinson, D., M. Humbert, R. Buhl, A. A. Cruz, H. Inoue, S. Korom, N. A. Hanania, and P. Nair. 2017. Revisiting type 2-high and type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin. Exp. Allergy* 47: 161–175.
118. Norling, L. V., A. L. Sampaio, D. Cooper, and M. Perretti. 2008. Inhibitory control of endothelial galectin-1 on in vitro and in vivo lymphocyte trafficking. *FASEB J.* 22: 682–690.
119. Sanchez-Cuellar, S., H. de la Fuente, A. Cruz-Adalia, A. Lamana, D. Cibrian, R. M. Giron, A. Vara, F. Sanchez-Madrid, and J. Ancochea. 2012. Reduced expression of galectin-1 and galectin-9 by leucocytes in asthma patients. *Clin. Exp. Immunol.* 170: 365–374.
120. Delbrouck, C., I. Doyen, N. Belot, C. Decaestecker, R. Ghanooni, A. de Lavareille, H. Kaltner, G. Choufani, A. Danguy, G. Vandenhoven, et al. 2002. Galectin-1 is overexpressed in nasal polyps under budesonide and inhibits eosinophil migration. *Lab. Invest.* 82: 147–158.
121. Sena, A. A., P. J. Provazzi, A. M. Fernandes, P. M. Cury, P. Rahal, and S. M. Oliani. 2006. Spatial expression of two anti-inflammatory mediators, annexin 1 and galectin-1, in nasal polyposis. *Clin. Exp. Allergy* 36: 1260–1267.
122. Yang, L. T., Q. Shu, X. Q. Luo, Z. Q. Liu, S. Q. Qiu, J. Q. Liu, H. J. Guo, L. J. Li, M. G. Li, D. B. Liu, et al. 2017. Long-term effects: Galectin-1 and specific immunotherapy for allergic responses in the intestine. *Allergy.* DOI: 10.1111/all.13256.
123. Blidner, A. G., and G. A. Rabinovich. 2013. 'Sweetening' pregnancy: galectins at the fetomaternal interface. *Am. J. Reprod. Immunol.* 69: 369–382.
124. Tirado-González, I., N. Freitag, G. Barrientos, V. Shaikly, O. Nagaeva, M. Strand, L. Kjellberg, B. F. Klapp, L. Mincheva-Nilsson, M. Cohen, and S. M. Blois. 2013. Galectin-1 influences trophoblast immune evasion and emerges as a predictive factor for the outcome of pregnancy. *Mol. Hum. Reprod.* 19: 43–53.
125. Kopcow, H. D., F. Rosetti, Y. Leung, D. S. Allan, J. L. Kutok, and J. L. Strominger. 2008. T cell apoptosis at the maternal-fetal interface in early human pregnancy, involvement of galectin-1. *Proc. Natl. Acad. Sci. USA* 105: 18472–18477.
126. Gómez-Chávez, F., V. Castro-Leyva, A. Espejel-Núñez, R. G. Zamora-Mendoza, H. Rosas-Vargas, J. C. Cancino-Díaz, M. E. Cancino-Díaz, G. Estrada-Gutierrez, and S. Rodríguez-Martínez. 2015. Galectin-1 reduced the effect of LPS on the IL-6 production in decidual cells by inhibiting LPS on the stimulation of IκBζ. *J. Reprod. Immunol.* 112: 46–52.
127. Woidacki, K., M. Popovic, M. Metz, A. Schumacher, N. Linzke, A. Teles, F. Poirier, S. Fest, F. Jensen, G. A. Rabinovich, et al. 2013. Mast cells rescue implantation defects caused by c-kit deficiency. *Cell Death Dis.* 4: e462.

128. Rabinovich, G. A., D. Gabrilovich, and E. M. Sotomayor. 2007. Immunosuppressive strategies that are mediated by tumor cells. *Annu. Rev. Immunol.* 25: 267–296.
129. Cedeno-Laurent, F., M. J. Opperman, S. R. Barthel, D. Hays, T. Schatton, Q. Zhan, X. He, K. L. Matta, J. G. Supko, M. H. Frank, et al. 2012. Metabolic inhibition of galectin-1-binding carbohydrates accentuates antitumor immunity. *J. Invest. Dermatol.* 132: 410–420.
130. Juszczynski, P., J. Ouyang, S. Monti, S. J. Rodig, K. Takeyama, J. Abramson, W. Chen, J. L. Kutok, G. A. Rabinovich, and M. A. Shipp. 2007. The AP1-dependent secretion of galectin-1 by Reed Sternberg cells fosters immune privilege in classical Hodgkin lymphoma. *Proc. Natl. Acad. Sci. USA* 104: 13134–13139.
131. Ouyang, J., P. Juszczynski, S. J. Rodig, M. R. Green, E. O'Donnell, T. Currie, M. Armant, K. Takeyama, S. Monti, G. A. Rabinovich, et al. 2011. Viral induction and targeted inhibition of galectin-1 in EBV+ posttransplant lymphoproliferative disorders. *Blood* 117: 4315–4322.
132. Ito, K., and S. J. Ralph. 2012. Inhibiting galectin-1 reduces murine lung metastasis with increased CD4(+) and CD8(+) T cells and reduced cancer cell adherence. *Clin. Exp. Metastasis* 29: 561–572.
133. Verschuere, T., J. Toelen, W. Maes, F. Poirier, L. Boon, T. Tousseyn, T. Mathivet, H. Gerhardt, V. Mathieu, R. Kiss, et al. 2014. Glioma-derived galectin-1 regulates innate and adaptive antitumor immunity. *Int. J. Cancer* 134: 873–884.
134. Baker, G. J., P. Chockley, D. Zamler, M. G. Castro, and P. R. Lowenstein. 2016. Natural killer cells require monocytic Gr-1(+)/CD11b(+) myeloid cells to eradicate orthotopically engrafted glioma cells. *OncoImmunology* 5: e1163461.
135. Soldati, R., E. Berger, A. C. Zenclussen, G. Jorch, H. N. Lode, M. Salatino, G. A. Rabinovich, and S. Fest. 2012. Neuroblastoma triggers an immunoevasive program involving galectin-1-dependent modulation of T cell and dendritic cell compartments. *Int. J. Cancer* 131: 1131–1141.
136. Cedeno-Laurent, F., R. Watanabe, J. E. Teague, T. S. Kupper, R. A. Clark, and C. J. Dimitroff. 2012. Galectin-1 inhibits the viability, proliferation, and Th1 cytokine production of nonmalignant T cells in patients with leukemic cutaneous T-cell lymphoma. *Blood* 119: 3534–3538.
137. Demotte, N., V. Stroobant, P. J. Courtoy, P. Van Der Smissen, D. Colau, I. F. Luescher, C. Hivroz, J. Nicaise, J. L. Squifflet, M. Mourad, et al. 2008. Restoring the association of the T cell receptor with CD8 reverses anergy in human tumor-infiltrating lymphocytes. *Immunity* 28: 414–424.
138. Wu, X., J. Li, E. M. Connolly, X. Liao, J. Ouyang, A. Giobbie-Hurder, D. Lawrence, D. McDermott, G. Murphy, J. Zhou, et al. 2017. Combined Anti-VEGF and Anti–CTLA-4 therapy elicits humoral immunity to galectin-1 which is associated with favorable clinical outcomes. *Cancer Immunol. Res.* 5: 446–454.
139. Lykken, J. M., M. Horikawa, V. Minard-Colin, M. Kamata, T. Miyagaki, J. C. Poe, and T. F. Tedder. 2016. Galectin-1 drives lymphoma CD20 immunotherapy resistance: validation of a preclinical system to identify resistance mechanisms. *Blood* 127: 1886–1895.
140. Fichorova, R. N., H. S. Yamamoto, T. Fashemi, E. Foley, S. Ryan, N. Beatty, H. Dawood, G. R. Hayes, G. St-Pierre, S. Sato, and B. N. Singh. 2016. *Trichomonas vaginalis* lipophosphoglycan exploits binding to galectin-1 and -3 to modulate epithelial immunity. *J. Biol. Chem.* 291: 998–1013.
141. Vasta, G. R., C. Feng, N. González-Montalbán, J. Mancini, L. Yang, K. Abernathy, G. Frost, and C. Palm. 2017. Functions of galectins as 'self/non-self'-recognition and effector factors. *Pathog. Dis.* DOI: 10.1093/femspd/ftx046.
142. Cagnoni, A. J., J. M. Pérez Sáez, G. A. Rabinovich, and K. V. Mariño. 2016. Turning-off signaling by siglecs, selectins, and galectins: Chemical inhibition of glycan-dependent interactions in cancer. *Front. Oncol.* 6: 109.