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Galectins: Key Players at the Frontiers of Innate and Adaptive Immunity

Verónica C. Martínez Allo[1]; Marta A. Toscano[1]; Nicolás Pinto[1]; and Gabriel A. Rabinovich[1, 2]

[1] Laboratorio de Inmunopatología. Instituto de Biología y Medicina Experimental (IBYME), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), C1428, Buenos Aires, Argentina
[2] Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales. Universidad de Buenos Aires, C1428, Buenos Aires, Argentina
FAX: +54–11–4786–2564, TEL: +54–11–4783–2869, E-mail: gabyrabi@gmail.com

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Abstract

The proper function of the immune system entails multiple regulatory pathways aimed at modulating immunogenic and tolerogenic functions of immune cells. Galectins, a family of carbohydrate-binding proteins, control a variety of biological processes involved in activation, differentiation, trafficking and survival of immune cells. In this review we summarize pioneer work and emerging findings highlighting selected functions of galectins as regulatory checkpoints that control innate and adaptive immune cell programs.

A. Introduction

The immune system is orchestrated by a coordinated network of cells and cytokines that ensures a delicate balance of host responses against microbial infections and tumors, controls sterile inflammation and protects against development of autoimmune responses. Proper execution of immune responses entails recruitment and activation of innate immune cells as well as activation, proliferation and differentiation of effector lymphocytes. However, this system is tightly controlled by a number of different regulatory pathways that counterbalance immune effector functions by repressing innate and adaptive immune programs and avoiding self tissue damage (1).

Galectins, a family of carbohydrate-binding proteins, have emerged as a new class of soluble molecules capable of stimulating or repressing a number of innate and adaptive immune processes. These endogenous lectins are synthesized within the cytoplasmic compartment and further exported to the extracellular milieu through mechanisms that are independent of the endoplasmic reticulum (ER) and Golgi apparatus (2). Interestingly, galectins play extracellular roles through interaction with a variety of glycoconjugates on the cell surface or extracellular matrix but can also function inside the cells by controlling intracellular processes, including autophagy, alternative splicing and intracellular trafficking *via* protein–protein or protein–glycan interactions (2).

Members of the galectin family are classified according to their structure into three different groups: 1) 'proto-type' galectins (galectin-1, 2, 5, 7, 10, 11, 13, 14, 15 and 16) which display one carbohydrate recognition domain (CRD) that can dimerize; 2) 'tandem-repeat' galectins (galectin-4, 6, 8, 9 and 12) which contain two homologous CRDs in tandem in a single polypeptide chain and 3) the chimera-type galectin-3 which uniquely displays a CRD connected to a non-lectin N-terminal region responsible for oligomerization (3). The multivalent nature of galectin–glycan interactions and the unique biochemical features of these proteins (*e.g.* sensitivity to oxidative inactivation, requirements for dimerization/oligomerization and carbohydrate-binding activity) dictate their biological activities. By recognizing poly-lactosamine (LacNAc) residues in complex *N*-glycans and core 2-*O*-glycans, galectins can modulate the activation, differentiation, trafficking and survival of immune cells by regulating clustering, internalization, and signaling of relevant glycosylated receptors (2, 4). In this review we summarize the main biological functions of galectins within innate and adaptive immune compartments and discuss possible mechanisms underlying these effects.

B. Galectin-1 (Gal1)

The immunomodulatory properties of Gal1 were originally inferred by its up-regulated expression in immune privileged sites (*e.g.* placenta, testis and tumors) and were further evidenced by the ability of this lectin to control pro-inflammatory cytokine synthesis, T-cell survival and immune cell activation (5, 6). These observations were reinforced by numerous publications describing the ability of exogenous Gal1 to suppress T-cell-mediated autoimmune diseases and the key role of this lectin in tumor-cell evasion of immune responses (6–13). Several studies have focused on the immunoregulatory effects of this endogenous lectin in a broad range of innate and adaptive immune functions (6).

One of the first documented effects of Gal1 was its ability to

induce apoptosis of thymocytes and activated T cells (14–16). Interestingly, several glycosylated receptors including CD45, CD43 and CD7 have been implicated as counter receptors for Gal1-induced cell death (17–19). However, despite preferential binding of Gal1 to particular glycosylated receptors, the ability of this lectin to interact with these glycoproteins ultimately depends on the cell's glycosylation machinery, particularly on a set of specific glycosyltransferases acting in concert to generate Gal1-specific glycoepitopes (20–22). In this regard, the cytokine milieu responsible for differentiating T helper subsets can also modulate the cell surface glycosylation profile and regulate Gal1 binding and apoptosis. While T helper (Th) 1 and Th17 effector cells express the repertoire of cell surface glycans that are required for Gal1 binding and the subsequent induction of cell death, Th2 cells are resistant to this effect due to the modification of β-galactosides with α2,6-linked sialic acid on cell surface glycoproteins (23). Thus, the selective elimination of Th1/Th17 cells may contribute to the polarization of the immune response towards the Th2/T regulatory (Treg) profiles observed in experimental models of autoimmunity and cancer. Interestingly, Gal1 activity is not only regulated by the presence or absence of specific glycan ligands, but it also relies on particular physicochemical properties of this protein, including the redox status (Gal1 exhibits an unusual number of 6 cysteine residues in its sequence) and the dimerization equilibrium of this protein. Thus, cell surface glycosylation, together with intrinsic biochemical properties of Gal1, dictate its biological activity and control the fate and function of polarized T cells. However, Gal1 may also trigger regulatory programs through mechanisms that are independent of its pro-apoptotic activity. Particularly, Gal1 promotes the expansion and recruitment of Treg cells in models of pregnancy, parasite infection, autoimmunity and breast cancer, highlighting its central immunoregulatory and pro-resolving activities (12, 24–26). Furthermore, Gal1 has been identified as a key effector molecule of the immunosuppressive function of Treg cells (27). In addition, Gal1 contributes to immunosuppression by directly interfering with T-cell adhesion and cytokine production (28). Moreover, Gal1 antagonizes TCR-transmitted signals promoting the contraction of the $CD8^+$ T cell compartment (29), inhibits IFN-γ synthesis in allogeneic T-cell reactions (30), and promotes IL-10 synthesis on $CD4^+$ T cells (31). Altogether, these evidences point to a major role of this lectin in re-calibrating T cell responses by controlling the survival, differentiation and activation of these cells (Fig. 1).

Studies aimed at elucidating the role of Gal1 within the B-cell compartment identified the ability of this lectin to form survival niches for developing B cells in the bone marrow. Gal1 produced

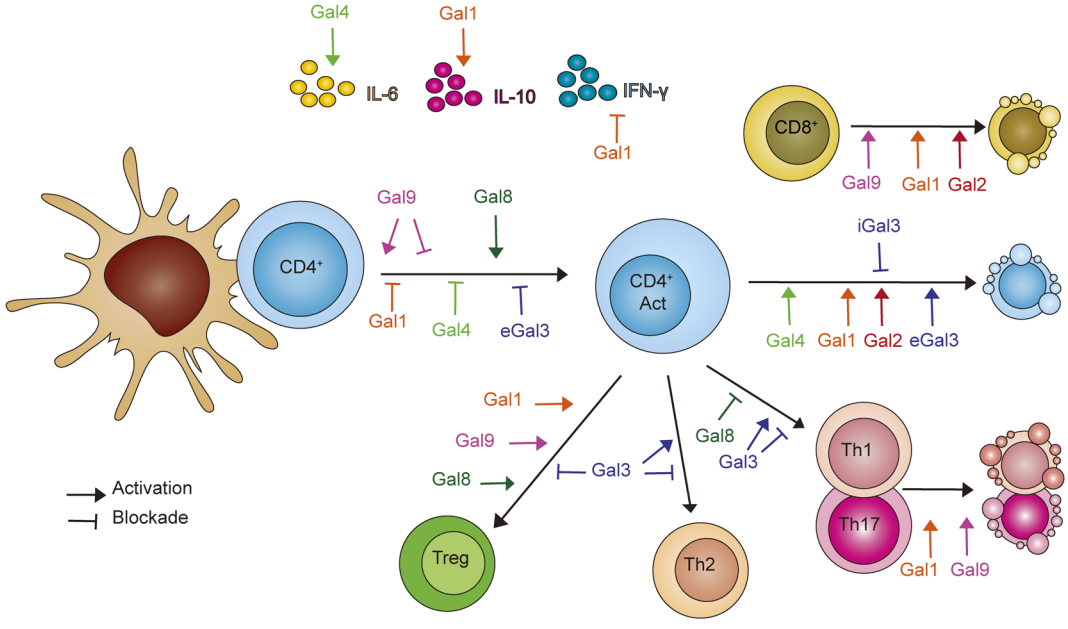

Fig. 1. Roles of galectins in the control of T-cell activation, differentiation and survival. **Gal1** inhibits T-cell activation, modulates cytokine secretion, promote Treg cell expansion and selectively deletes $CD8^+$ activated T cells and fully differentiated Th1 and Th17 cells. **Gal2** reduces lamina propria T cells and $CD8^+$ T cell survival. Extracellular **Gal3** (eGal3) reduces-cell viability and increases the threshold of T-cell activation. However, intracellular Gal3 (iGal3) can prevent Fas-mediated apoptosis. Moreover, Gal3 exerts variable effects on regulating Th1, Th2, and Th17 responses depending on the nature of the stimuli and different physiologic or pathologic conditions. In addition Gal3 inhibits differentiation of Tregs cells in the context of autoimmune disorders. **Gal4** induces apoptosis of mucosal T cells and increases IL-6 secretion. **Gal8** promotes activation of T cells and induces a bias toward a Treg cell phenotype. **Gal9** reduces the viability of Th1-differentiated cells and tumor-infiltrating $CD8^+$ T cells and promotes the expansion of Treg cells. This lectin induces T-cell death or T cell activation depending on its relative concentration and prevalent microenvironment.

by stromal cells interacts with the pre-BCR, and $\alpha 4\beta 1$, $\alpha 5\beta 1$, and $\alpha 4\beta 7$ integrins leading to the formation of a dynamic synapse between pre-BII lymphocytes and stromal cells. This interaction triggers pre-BCR signaling and promotes pre-BII cell survival; central events for efficient progression across the B-cell differentiation pathway (32–34). In peripheral mature B cells, Gal1 influences B-cell proliferation, BCR-mediated signaling and immunoglobulin production during plasma cell differentiation, indicating key roles of this lectin during B-cell maturation, proliferation and differentiation (35, 36).

Cells of the myeloid lineage are essential components of the innate immune system. By sensing pathogen-associated molecular partners (PAMPs) and danger-associated molecular partners (DAMPs) these cells can trigger inflammatory cascades that ultimately tailor adaptive immune responses. In this context, the Gal1-glycan axis was reported to modulate several biological functions of neutrophils, macrophages and dendritic cells (2). Particularly, early studies in models of acute inflammation demonstrated a central role of Gal1 in regulating the migratory capacity of neutrophils by inhibiting their adhesion to activated endothelial cells in response to inflammatory cues. However, in the absence of an inflammatory process, Gal1 can actively recruit neutrophils by interacting with CD43, a major *O*-glycosylated mucin (37). Interestingly, Gal1 can also regulate turnover and removal of neutrophils by inducing phosphatidilserine exposure on the cell surface without displaying alterations in membrane morphology, DNA fragmentation or cell cycle progression (38). These observations underscore the ability of Gal1 to regulate neutrophil function either during acute inflammation or in steady-state conditions.

In addition to modulating the neutrophil compartment, Gal1 also controls the phagocytic activity, antigen presentation capacity and polarization profile of monocytes and macrophages. In particular, Gal1, either exogenously provided or endogenously regulated, inhibits mayor histocompatibility complex (MHC) II expression on macrophages and decreases the ability of these cells to stimulate allogeneic T-cell responses by regulating ERK1/2 signaling pathway (39). In addition, Gal1 inhibits lipopolysaccharide (LPS)-induced nitric oxide production and inducible nitric oxide synthase (iNOS) expression and shifts the balance towards activation of L-arginase, the alternative metabolic pathway of L-arginine, promoting M2 macrophage polarization; this effect ultimately leads to the resolution of inflammatory responses (40). In line with this evidence, in a context of autoimmune central nervous system inflammation, Gal1 de-activates microglial cells and promotes a shift toward an M2 phenotype through glycosylation-dependent interactions with core 2 *O*-glycans on CD45 (41). Furthermore, this endogenous lectin promotes conversion of peritoneal macrophages toward a pro-resolving profile during induction of peritonitis (41, 42).These observations support a pivotal role of Gal1 in regulating macrophage and microglial functions in the context of acute and chronic inflammation.

Dendritic cells (DCs) are phenotypically and functionally diverse cells capable of orchestrating an effective immune response, polarizing T-cells and triggering regulatory circuits that safeguard immunological tolerance and homeostasis. A number of reports highlight a major role for Gal1 in DC activation, migration and differentiation. In particular, Gal1 interaction with CD43 and CD45 on monocyte-derived DCs, promotes their migration across extracellular matrix through signaling pathways involving Syk and protein kinase C(43, 44). In fact, deposition of Gal1 on the extracellular matrix constitutes a triggering signal for migration of specific human DCs subsets, favoring migration of immunogenic, but not tolerogenic DCs across lymphatic endothelial cells (45). In addition to regulating DC trafficking, Gal1 also promotes differentiation of IL-27-producing tolerogenic DCs which in turn induce IL-10-secreting Foxp3$^-$ regulatory T (Tr1) cells during autoimmunity and cancer settings (46). This effect was substantiated in the context of parasite infection, showing that *Trypanosoma cruzi* triggers a Gal1-driven regulatory circuit mediated by tolerogenic DCs and Foxp3$^+$ Treg cells which contribute to perpetuate parasite infection and chronic disease (25). Moreover, recent studies suggest that *Yersinia entercolitica*, an enteropathogenic bacterium subverts innate and adaptive immunity *via* Gal1-mediated mechanisms (47). Thus, Gal1 represses innate and adaptive immune cell programs *via* glycosylation-dependent mechanisms involving impairment of T-cell activation, differentiation and survival, inhibition of neutrophil recruitment, polarization of macrophages toward an M2 profile and induction of tolerogenic DCs. By triggering these broad immunomodulatory effects, Gal1 serves as an emerging regulatory checkpoint that shapes the immune landscape in settings of autoimmunity, infection, allergy and cancer. In this regard, tumors may co-opt Gal1 to de-articulate antitumor immune responses (4, 26), promote hypoxia-driven angiogenesis (48–50) and link commensal microbiota to tumor-promoting inflammation and immunosuppression (51, 52). Moreover, Gal1 contributes to resolution of allergic airway inflammation by modulating eosinophil survival, adhesion and trafficking (53). Thus, Gal1 functions as a resolution-associated molecular partner that preserves immune tolerance and counteracts pro-inflammatory signals in a wide range of pathologic conditions.

C. Galectin-2 (Gal2)

Gal2 is a member of the prototype group of galectins structurally related to Gal1, nonetheless these galectins differ in their tis-

sue distribution (54). Gal2 is preferentially expressed on epithelial cells of the gastrointestinal tract suggesting a potential role for this lectin in the regulation of mucosal immunity (55). In this regard, administration of recombinant Gal2 ameliorates clinical manifestations of experimental colitis by impairing viability of lamina propria T cells (55). Consistently, Gal2 suppress contact allergy by eliminating activated $CD8^+$ T cells (56) (Fig. 1). The pro-apoptotic function of Gal2 requires recognition of β1 integrin (CD29), but not CD3 or CD7 (55). Similar to Gal1, Gal2 induces exposure of phosphatidylserine in activated neutrophils, highlighting its potential contribution to clearance of these cells following excessive activation (57). Interestingly, Gal2 promoted M1 macrophage polarization through CD14/ Toll-like receptor (TLR)4 cross-linking (58). Thus, although Gal1 and Gal2 share the ability to control T cells and neutrophils, these closely-related galectins exert opposite functions within the macrophage compartment. Further studies in mice lacking Gal2 are needed to elucidate the *in vivo* role of this endogenous lectin in physiologic and pathologic settings.

D. Galectin-3 (Gal3)

Gal3, the unique chimera-type member of the galectin family, is ubiquitously expressed and exerts a broad range of biological functions depending on its intra- or extracellular localization. Similar to other galectins, Gal3 has been implicated in the control of T-cell activation, cytokine secretion and survival. In particular, Gal3 regulates the signaling threshold of T cells by modulating the lateral compartmentalization of transmembrane glycoproteins. The TCR as well as many other cell surface receptors carry complex *N*-glycan structures modified by the *N*-acetylglucosaminyltransferase 5 (Mgat5), an enzyme responsible for generating the β1,6 *N*-acetylglucosamine branches on *N*-glycans. Importantly, Mgat5-deficient mice develop enhanced delayed-type hypersensitivity reactions, greater susceptibility to autoimmune diseases and increased Th1 polarization (59, 60). The proposed mechanisms underlying these exacerbated immune reactions involve regulation of receptor distribution by the formation of Gal3/*N*-glycan supramolecular structures, often called 'lattices' on the surface of T cells. These interactions counteract actin microfilaments and regulate the relative proportion of CD45 *versus* TCR/CD4/Lck occupancy on GM1-enriched microdomains (61). Thus, Gal3 can modulate the threshold for TCR activation and signaling by controlling the distribution of cell surface glycoproteins.

In addition to these regulatory properties, extracellular Gal3 has also been involved in the modulation of T-cell survival. This lectin induces apoptosis of human leukemia T cell lines and activated T cells through carbohydrate-dependent interactions with CD45, CD7 and CD29 glycoproteins (62, 63). On the contrary, intracellular Gal3 negatively regulates T-cell death. Specifically, T cells overexpressing Gal3 displayed reduced susceptibility to Fas-induced apoptosis through mechanisms involving interaction with members of the Bcl-2 protein family (64).

In addition to regulating T-cell activation and survival, Gal3 also modulates cytokine synthesis and T-cell differentiation in the context of autoimmune diseases and allergy. Mice lacking Gal3 ($Lgals3^{-/-}$) displayed reduced synthesis of Th1 and Th17 cytokines and expansion of Th2 and Treg cell phenotypes, attenuating disease severity in experimental models of autoimmune encephalomyelitis, antigen-induced arthritis and concanavalin A-induced hepatitis (65–67). However, in experimental allergic disease, $Lgals3^{-/-}$ mice display increased Th1 responses associated to augmented IL-12 production by dendritic cells (DCs) (68). These controversies are also reflected in infection models: Fermino and colleagues described an increased frequency of Tregs and no changes in the Th1/Th2 balance in $Lgals3^{-/-}$ mice during *Leishmania major* infection (69, 70), whereas these mice display an increased Th1 differentiation profile in response to other parasites including *Toxoplasma gondii* or *Schistosoma mansoni* (71, 72). Thus, Gal3 exerts different immumodulatory activities on T helper cell differentiation and cytokine production, effects that are directly associated to the nature and magnitude of immune responses triggered by each specific pathogen (Fig. 1).

Interestingly, within tumor microenvironments, Gal3 suppresses antitumor immunity by contributing to T-cell anergy and exhaustion (73). Mechanistically, this lectin helps distancing the TCR from CD8 molecules (73), impairs LFA-1-mediated immunological synapse (74) and inhibits IFN-γ diffusion within the tumor-extracellular matrix reducing chemokine gradients and T cell infiltration (75). Moreover, this lectin has been proposed to serve as a ligand of the checkpoint receptor lymphocyte activation gene-3 (LAG-3) promoting contraction of the $CD8^+$ T cell compartment (76). Thus, Gal3 contributes to restrain antitumor immunity *via* glycosylation-dependent modulation of tumor-infiltrating lymphocytes.

Within the B cell compartment, Gal3 contributes to B-cell differentiation and survival. Particularly, intracellular Gal3 mediates the anti-apoptotic effect of IL-4 and favors B-cell commitment toward a memory phenotype (77). Furthermore, this lectin inhibits B1 cell differentiation into plasma cells in the peritoneal cavity and mesenteric lymph nodes of *Schistosoma mansoni*- and *Trypanosoma cruzi*-infected mice (77–79). Thus, Gal3 favors transition toward a memory B cell phenotype and controls parasite infection *in vivo*. This conclusion is in agreement with the observation that Gal3 deficiency reduces parasite load in experimental *Plasmodium yoelii* infection by augmenting anti-*P. yoelii* IgG2b

antibodies (80). Further studies are needed to fully understand the impact of Gal3 and specific glycans on B-cell fate and the consequences of these interactions in physiological and pathological conditions.

In myeloid cells, Gal3 plays multifunctional roles by regulating cellular activation, trafficking, differentiation and survival (2). In particular, Gal3 induces neutrophil migration in *Leishmania major and Streptococcus pneumoniae* infection models (81, 82). Likewise, this lectin promotes adhesion and increased motility of mast cells on fibronectin-coated plates and is necessary for effective recruitment of DCs to draining lymph nodes after sensing maturation signals (83, 84). Furthermore, this chimera-type lectin augments activation and phagocytic activity of neutrophils promoting clearance of pneumococcal infections (85). However, Gal3 can act in concert with soluble fibrinogen to induce activation and reduce survival of neutrophils (86). In mast cells, experiments involving *Lgals3*$^{-/-}$ mice and shRNA silencing strategies demonstrated opposing roles for Gal3 on the release of inflammatory mediators by these cells (83, 87). Thus, Gal3 controls myeloid cell migration exerting both positive and negative roles in neutrophil and mast cell biology. Whether intracellular or extracellular functions of this lectin prevail in each individual effect remains to be explored.

Gal3 exerts diverse functions within the macrophage compartment. In particular, macrophages from *Lgals3*$^{-/-}$ mice display reduced phagocytic capacity and impaired IL-4/IL-13-mediated alternative activation (88, 89). In this regard, this lectin can activate its own expression and secretion, promoting a positive feedback loop that maintains an M2-type polarization profile (89). However, other reports showed that *Lgals3*$^{-/-}$ mice display reduced thioglycolate-induced inflammatory responses in the peritoneal cavity and exhibited lower expression of pro-inflammatory cytokines (90). Within the CNS, Gal3 contributes to activation and proliferation of microglial cells through mechanisms involving activation of insulin growth factor receptor (IGFR) and/or TLR4 during ischemia and neuroinflammation (91, 92). Furthermore, *Lgals3*$^{-/-}$ mice displayed reduced microglia activation and lower expression of the phagocytic receptor TREM2b in response to cuprizone-induced demyelination (93). Altogether, these reports highlight essential roles of Gal3 in positively or negatively regulating activation of macrophages and microglial cells and suggest their contribution to amplification of CNS inflammation or healing processes in injured tissues. Thus, Gal3 controls the fate and function of neutrophils, mast cells, macrophages and DCs by regulating their maturation, activation and migration, finally dictating the course of an adaptive immune response.

E. Galectin-4 (Gal4)

Similar to Gal2, Gal4 displays a tissue-specific distribution being preferentially localized on epithelial cells of the gastrointestinal tract (94, 95). This tandem repeat-type galectin has also been involved in the regulation of the T-cell viability (Fig. 1). In particular, Gal4 reduces intestinal inflammation by inducing apoptosis of mucosal T cells and reducing pro-inflammatory cytokine secretion (96). However, this lectin was also reported to induce IL-6 production in T cells through PKCϕ-dependent pathways, leading to stimulation of an intestinal inflammatory response (97) (Fig. 1). Similar to Gal1 and Gal2, Gal4 was also involved in regulating phosphatidylserine exposure on neutrophils with important implications in the homeostatic removal of these cells after the completion of their effector functions (57). Interestingly, Mathieu *et al.* studied galectin expression in normal and inflamed mucosal tissues reporting important variations in the expression of Gal4 in models of inflammatory bowel disease (98). Thus, controversial findings associated to pro- or anti-inflammatory roles of Gal4 during intestinal inflammation could be associated to the experimental model analyzed, the mouse strains employed, specific housing conditions and predominant microbiota. Further studies in Gal4-deficient mice are required to fully elucidate the role of endogenous Gal4 during inflammatory responses.

F. Galectin-8 (Gal8)

Gal8, a member of the subfamily of tandem-repeat galectins, exhibits wide tissue distribution and similar to other members of the galectin family plays key roles in the regulation of proliferation, activation and survival of immune cells (Fig. 1). In particular, Gal8 induces apoptosis of $CD4^+CD8^+$ thymocytes and human leukemia T cell lines through the activation of phosphatidic acid and ERK1/2 signaling pathways and the induction of the death receptor FasL (99, 100). On the other hand, Tribulatti *et al.* showed that Gal8 can positively regulate CD4 T cell proliferation by providing positive co-stimulatory signals without skewing the Th1/Th2 balance (101). Gal8 has been also studied in the context of autoimmunity; therapeutic administration of recombinant Gal8 ameliorates clinical signs of experimental autoimmune uveitis by promoting Treg differentiation and blunting pathogenic Th17 responses (102, 103). Mechanistically, Gal8 may influence activation and survival of effector T cells or regulate expansion of Treg cells through glycosylation-dependent mechanisms involving association with non-sialylated or α2,3-sialylated glycans.

Early studies performed by Nishi and colleagues revealed a central role for Gal8 in promoting neutrophil adhesion and activation by cross-linking integrin receptors (104). Notably, soluble Gal8 enhanced adhesion and superoxide production in neutrophils

through binding to integrin α_M (104). Moreover, recent studies revealed a central role of Gal8 on DC biology: bone marrow-derived DCs (BMDCs) treated with exogenous Gal8 exhibited a mature immunogenic phenotype capable of stimulating antigen-specific T-cell responses and promoting the synthesis of pro-inflammatory cytokines and chemokines including IL-6, TNF, MCP-1, and MCP-5. Furthermore, DCs from Gal8-deficient (*Lgals8*$^{-/-}$) mice displayed diminished CD86 and IL-6 expression and impaired ability to promote antigen-specific CD4$^+$ T cell activation (105). Thus, like other members of the family, Gal8 exerts either immunosuppressive or immunostimulatory functions on different cell types and different physiologic or pathologic conditions.

G. Galectin-9 (Gal9)

Gal9, a tandem-repeat member of the galectin family with wide tissue distribution, displays potent immunoregulatory activities toward lymphoid and myeloid cells (reviewed by Hirashima *et al.*, in this issue). This lectin controls viability of Th1-differentiated cells and tumor-infiltrating CD8$^+$ T cells by interacting with the Tim-3 inhibitory receptor *via* glycosylation-dependent mechanisms (106–110). However, the role of Gal9 in T-cell biology is not exempt from controversies. Gooden *et al.* described that Gal9, at low doses (nM range) induces T-cell activation and expansion on resting human T cells (111). Furthermore, Gal9 can trigger signaling events that activate T cells in an antigen-independent manner (107). Interestingly, in these studies Gal9 induced T cell death in a great proportion of cells *in vitro*, but those surviving cells experienced activation and expansion (107, 111). Moreover, Gal9 can also regulate the polarization and differentiation of immune cells. In particular, this endogenous lectin inhibits Th1- and Th17-mediated responses in models of arthritis, glomerulonephritis, and encephalomyelitis (108, 112, 113). Furthermore, this lectin contributes to polarization of macrophages towards an M2 phenotype in samples of advanced melanoma patients (114). In this regard, recent studies identified a central role of Gal9 as a major ligand of Dectin-1 in macrophages from pancreatic cancer patients endowing these cells with an immunosuppressive pro-tumorigenic phenotype (115). The immunosuppressive functions of Gal9 were reinforced by additional studies indicating that this lectin is critical for the induction, stability and suppressive activity of Treg cells (113, 116). The mechanisms underlying these effects involve the interaction of Gal9 with CD44 and the formation of cell surface complexes with TGF-β receptor 1 (117). Thus, Gal9 fine-tunes immune signaling programs leading to Tim-3-dependent or independent apoptosis of Th1 cells, CD44-mediated expansion of Treg cells and Dectin-1-dependent modulation of macrophage function (Fig. 1).

H. Other Galectins

Although there is still much to be learned on the immunoregulatory activities of other galectins, emerging evidence implicate Gal10, a proto-type member of the family, as an intracellular mediator of the immunosuppressive activity of Treg cells and eosinophils (118, 119). Moreover, extracellular Gal7 induced T-cell apoptosis whereas intracellularly this lectin controlled proliferation and differentiation of keratinocytes through mechanisms involving the JNK1, miR-203 and p63 signaling pathways (120–122). Enforced expression of Gal7 in cancer cells controlled several molecular networks involved in metabolism, survival and immunity (123). On the other hand Gal12, a tandem-repeat galectin preferentially expressed in adipose tissue, triggers an inflammatory response through polarization of macrophages towards an M1 profile (124). Furthermore, Gal13, Gal14 and Gal16 have been predominantly described in placental tissues, suggesting their potential roles in immune tolerance mechanisms at the maternal-fetal interface (125).

I. Concluding Remarks

In this review we summarized selected findings on the role of galectins in the regulation of innate and adaptive immune responses and its implications in the development and resolution of autoimmunity, infection, allergy and cancer. Although galectins exert multiple functions on immune cells, some general conclusions can be drawn from many years of research in the field. First, it is clear that some members of this family including Gal1 and Gal9 display predominant immunosuppressive effects, while other members like Gal3 and Gal8 have dual pro- or anti-inflammatory activities. These variable functions could be associated to intracellular *versus* extracellular activities of these proteins (126), different roles of endogenous *versus* exogenous galectins and subtle differences in glycan-binding preferences of individual members of the family (2, 127). In this regard, although different galectins share a common structural fold and are defined as β-galactoside binding lectins, individual members of the family display fine specificities for particular substitutions and modifications in the lactosamine core particularly the presence of terminal sialic acid residues (127, 128). These glycan structures are differentially regulated in response to pro- or anti-inflammatory stimuli, hypoxic or acidic microenvironments and the metabolic status of target cells. The complexity of this scenario increases as we consider galectin expression pattern and tissue distribution. While some galectins have a wide tissue distribution (*e.g.* Gal1 and Gal3), others are preferentially distributed on specific cells and tissues (*e.g.* Gal4, Gal12), suggesting that more than one galectin might be expressed in a given tissue competing for common glycosylated ligands. Additional studies aimed

at analyzing specific roles of endogenous galectins *in vivo* and their possible overlapping activities will contribute to dissect their most important functions in different tissues and their implications in immunopathology. Understanding these pathways will help delineate rational therapies aimed at selectively targeting or reinforcing expression of individual galectins in different pathologic conditions including autoimmunity, allergy, infection and cancer.

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Information of the Authors

Gabriel Rabinovich was born in Córdoba, Argentina in 1969 and obtained his first degree in Biochemistry (1993) and his Ph.D. in Immunology (1999) from the School of Chemical Sciences at the National University of Córdoba. He has mentored numerous Ph.D. and post-doctoral fellows, served on the editorial board of several journals, held visiting professorships at international universities and is member of the US National Academy of Sciences (NAS), the Third World Academy of Sciences (TWAS), the Latin American Academy of Sciences (ACAL) and the Argentinean Academy of Sciences (ANC). He is Senior Investigator of the National Research Council (CONICET) and Professor of Immunology at the School of Exact and Natural Sciences, University of Buenos Aires. He currently heads the Division of Immunopathology at the Institute of Biology and Experimental Medicine (IBYME) and is Deputy Director of IBYME. Gabriel Rabinovich won several awards including the Simon Guggenheim Award (USA), The Third World Academy of Science Prize in Biomedical Sciences (Italy), the Bunge & Born Award in Biomedical Sciences (Argentina) and the Bernardo Houssay Award (Argentina). Rabinovich's laboratory is interested in understanding the function of glycans and glycan-binding proteins in cellular processes relevant to immune regulation, tolerance and angiogenesis in health and disease. Using an interdisciplinary approach, they have demonstrated that endogenous galectins, a family of soluble glycan-binding proteins, can translate glycan-encoded information into novel regulatory programs that control inflammation, suppress autoimmune pathology and allow cancer cells to evade immune responses and promote blood vessel formation. These findings opened new possibilities for development of therapeutic strategies aimed at potentiating antitumor responses, limiting autoimmune inflammation and overcoming aberrant angiogenesis.