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Review

Review

Tissue-specific control of galectin-1-driven circuits during inflammatory responses

Anabela M Cutine[2,†], Camila A Bach[2,†], Florencia Veigas[2,†], Joaquín P Merlo[2,†], Lorena Laporte[2,†], Montana N Manselle Cocco[2,†], Mora Massaro[2,†], Nicolas Sarbia[2,†], Ramiro M Perrotta[2,†], Yamil D Mahmoud[2,†] and Gabriel A Rabinovich[1,2]

[2]Instituto de Biología y Medicina Experimental (IBYME), Laboratorios de Inmunopatología, Glicómica Funcional e Inmuno-Oncología Translacional, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), C1428 Buenos Aires, Argentina

[1]To whom correspondence should be addressed: Tel: +54-11-4783-2869 (ext 266); e-mail: gabyrabi@gmail.com or gabriel.r@ibyme.conicet.gov.ar

[†]These authors, listed in alphabetical order, contributed equally to this work.

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Abstract

The relevance of glycan-binding protein in immune tolerance and inflammation has been well established, mainly by studies of C-type lectins, siglecs and galectins, both in experimental models and patient samples. Galectins, a family of evolutionarily conserved lectins, are characterized by sequence homology in the carbohydrate-recognition domain, atypical secretion via an endoplasmic reticulum–Golgi-independent pathway and by the ability to recognize β-galactoside-containing saccharides. Galectin-1 (Gal-1), a prototype member of this family, displays mainly anti-inflammatory and immunosuppressive activities, although, similar to many cytokines and growth factors, it may also trigger paradoxical pro-inflammatory effects under certain circumstances. These dual effects could be associated to tissue-, time- or context-dependent regulation of galectin expression and function, including particular pathophysiologic settings and/or environmental conditions influencing the structure of this lectin, as well as the availability of glycosylated ligands in immune cells during the course of inflammatory responses. Here, we discuss the tissue-specific role of Gal-1 as a master regulator of inflammatory responses across different pathophysiologic settings, highlighting its potential role as a therapeutic target. Further studies designed at analyzing the intrinsic and extrinsic pathways that control Gal-1 expression and function in different tissue microenvironments may contribute to delineate tailored therapeutic strategies aimed at positively or negatively modulating this glycan-binding protein in pathologic inflammatory conditions.

Key words: autoimmunity, cancer, chronic inflammation, galectin-1, glycoimmunology

Introduction

A myriad of pathologic conditions, including infectious, metabolic, neurodegenerative, autoimmune and malignant diseases, share the common denominator of excessive inflammation as a critical component responsible for the pathogenesis and evolution of the disease (Serhan et al. 2020). Genetic and environmental factors are the key determinants that govern the clinical outcome of autoimmune and chronic inflammatory disorders, ultimately leading to the loss of immune tolerance and disruption of homeostatic mechanisms. On the other hand, tumorigenesis and metastasis have been linked to chronic inflammation due to the prevalence of pro- and anti-inflammatory cytokines, chemokines and growth factors acting locally or systemically to modulate cancer progression (Arnold et al. 2015). The innate and adaptive immune mediators play critical roles either by orchestrating or dismantling inflammatory responses that take place in these pathological settings. Given the context-dependent regulation of different tissue microenvironments, distinct cytokines, alarmins and growth factors could be endowed with either pro- or anti-inflammatory properties in a spatio-temporal fashion, highlighting the dynamic plasticity of inflammatory responses (Serhan et al. 2020). To illustrate this concept, interleukin (IL)-17, a major pro-inflammatory cytokine that triggers pathogenic T helper (Th)17 cells in autoimmune diseases, displays paradoxical regulatory effects in the gut microenvironment (Hovhannisyan et al. 2011). Moreover, tumor necrosis factor (TNF), a master pro-inflammatory cytokine, may also display host protective responses depending on the extent of inflammation and the implicated signaling receptor (Eliçabe et al. 2010). Finally, the paradoxical anti- or pro-inflammatory role of cytokines during immune checkpoint blockade therapies may depend on whether they act before or after the application of these treatments (Hill et al. 2020). Thus, understanding the molecular and cellular mechanisms that control the course of inflammatory responses in different tissues is of vital importance for the development of tailored immunomodulatory therapies.

It has been well established that glycans, in their whole complexity, are present on all cells and their associated extracellular matrix (ECM). They play crucial roles by modulating cell differentiation, communication, vascularization and immunity across different tissues (Ohtsubo and Marth 2006; Bard and Chia 2016). The immune system harnesses the vast amount of information stored in glycan structures from different immune cell types and pathogens to control its activation, differentiation and homeostasis (Ohtsubo and Marth 2006). These structures, covalently linked to proteins and lipids to form glycoconjugates, are assembled hierarchically by the coordinated action of glycosyltransferases and glycosidases, which are differentially regulated in different cells and tissues. Protein N-glycosylation starts co-transcriptionally in the endoplasmic reticulum (ER), with the addition of a preformed oligosaccharide precursor to specific asparagine residues; further processing of *N*-glycans takes place in the ER and later in the Golgi. Meanwhile, biosynthesis of mucin-type *O*-glycans starts with the addition of an *N*-acetylgalactosamine (GalNAc) residue to serine or threonine, and Golgi-resident enzymes further modify this initial *O*-GalNAc structure, producing different core *O*-glycans. Once assembled, glycoproteins encode relevant information specifically deciphered by different families of dedicated glycan-binding proteins (Cummings 2009).

In the era of multiomics, "glycomics" arises as an exciting multidisciplinary challenge, focused on decoding glycocodes associated with multiple cell processes. In fact, the association of cellular glycans (glycophenotype) with a particular inflammatory condition has been essential to put forward the concept of a "tissue-specific" and "disease-specific" glycome that could be capitalized for therapeutic purposes (Ohtsubo and Marth 2006). High variability of glycan structures, due to several combinatorial possibilities, results in a major source of biological information and diversity. On top of this, the glycophenotype expressed by each given cell type is not only dependent on the cellular activation and differentiation status (Freire-de-Lima 2014) but is also regulated in a cell type- and tissue-specific fashion (Boscher et al. 2011; Nio-Kobayashi 2017). As glycans are commonly located on the cell surface, they represent the first contact point during cellular communication, making them central regulators of several metabolic and biochemical processes (nutrient availability, hypoxia and redox status) as well as environmental insults (pathogens, toxins and injuries) (Duan and Paulson 2020). Moreover, under chronic inflammation, some glycan structures that are commonly absent or present at low concentrations at steady-state conditions may vary their expression patterns and composition (Albrecht et al. 2014). In this context, a range of glycan-binding proteins, including C-type lectins, siglecs and galectins, can recalibrate immune cell homeostasis and rewire several signaling pathways in distinct immune cells and tissues, thus aggravating or attenuating the inflammatory response (Rabinovich and Croci 2012). These features make lectins and glycans attractive therapeutic targets and potential biomarkers in several pathophysiologic conditions (Cagnoni et al. 2016; Toscano et al. 2018).

Galectins are among the best-studied glycan-binding proteins implicated in the regulation of inflammatory responses (Toscano et al. 2018). They constitute a family of soluble proteins released to the extracellular medium through an alternative route which does not involve transit through the conventional ER–Golgi secretory pathway (Cummings 2009; Popa et al. 2018). Although the underlying mechanism of secretion of these proteins still remains a mystery, it appears to involve accumulation of galectins in patches beneath the plasma membrane, externalization through extracellular vesicles (Popa et al. 2018) and activation of inflammatory death pathways, including pyroptosis and necroptosis (Russo et al. 2021). Galectins are capable of interacting with a wide range of glycosylated receptors through protein–glycan or protein–protein interactions in a broad spectrum of cell types and tissues (Rabinovich and Toscano 2009). Although most research has been done in mammalian cells, where 15 members of the galectin family and other galectin-related members (e.g. Galectin related inter fiber protein (GRIFIN)) have been described, there is also evidence of galectin-like domains in insects, fungi, viruses and plants (Yang et al. 2008; Vasta et al. 2017). In addition to extracellular functions, galectins can also modulate intracellular events, including lymphocyte survival, autophagy and regulation of the splicing machinery (Rabinovich et al. 2007; Yang et al. 2008; Rabinovich and Toscano 2009; Brinchmann et al. 2018). The most conserved feature of galectins is the presence of at least one carbohydrate-recognition domain (CRD) comprised of 130 highly preserved amino acids which can be present in different configurations leading to three main galectin subfamilies: (1) "prototype" galectins (galectin-1 [Gal-1], -2, -5, -7, -10, -11, -13, -14 and -15) containing a single CRD that can occur as monomers or noncovalent dimers; (2) "tandem repeat-type" galectins (Gal-4, -6, -8, -9 and -12), which have two CRDs in tandem within the same polypeptide chain connected by a linker of 70 amino acids and (3) "chimera-type" galectins, with Gal-3 being the only member described so far, which has a single C-terminal CRD together

with a nonlectin N-terminal region that allows its oligomerization (Rabinovich et al. 2007; Yang et al. 2008).

Galectins are defined by their ability to recognize β-D-galactosyl-(1–4)-*N*-acetyl-D-glucosamine (*N*-acetyllactosamine [LacNAc]), a disaccharide, present in *N*- and *O*-glycans on cell surface glycoproteins (Barondes et al. 1994; Hirabayashi et al. 2002). However, it has been recently shown that galectins' CRDs can differ in amino acid sequences outside conserved sites, thus providing the ability to recognize diverse glycan structures (Thiemann and Baum 2016). Furthermore, modifications on LacNAc or poly-LacNAc structures may alter galectin–glycan interactions. For instance, some galectins can tolerate the addition of a terminal sialic acid or the addition of internal fucose in the LacNAc sequence, while others may lose their ability to bind LacNAc in the presence of such modifications (Kamili et al. 2016; Thiemann and Baum 2016). In this regard, we have recently found that Gal-12, a lectin preferentially expressed in adipose tissue, specifically binds to 3′-fucosylated structures (Maller et al. 2019). In addition, galectins may differ in their ability to recognize LacNAc in a terminal position or internal repetitions within the glycan structure. This relative selectivity may explain the functional variations observed among individual galectin family members (Hirabayashi et al. 2002; Stowell et al. 2008). Several factors can influence the biological activity of galectins, including their dimerization or oligomerization status, selective exposure of *N*- and *O*-glycans on target cells and the redox status of different tissue microenvironments (Rabinovich and Toscano 2009). Finally, while some galectins show a ubiquitous expression pattern (e.g. Gal-1 and Gal-3), others exhibit a preferential distribution in selected tissues (e.g. Gal-7 or Gal-12) (Nio-Kobayashi 2017).

Gal-1, a proto-type member of the galectin family, plays key immunoregulatory roles in autoimmunity and chronic inflammation. This lectin, composed of subunits of 14.5 kDa, occurs in a dynamic dimerization equilibrium (Camby et al. 2006). Increased concentrations allow dimer formation, which favors ligand binding and protects it from oxidative inactivation (Stowell et al. 2009). In this regard, Gal-1 is known to be intrinsically sensitive for oxidation, given the presence of an unusual number of six cysteine residues within its sequence, leading to rapid lectin inactivation after purification, unless it is preserved in the presence of a reducing agent (Abbott and Feizi 1991; Hirabayashi and Kasai 1991; Stowell et al. 2009; Guardia et al. 2014). Gal-1 can bind to terminal LacNAc structures present in complex, branched *N*-glycans and core-2 *O*-glycans (Hirabayashi et al. 2002; Patnaik et al. 2006; Rabinovich and Toscano 2009). However, terminal α(2,6)-linked sialic acid added to terminal LacNAc units hinders Gal-1 binding (Thiemann and Baum 2016). Thus, diverse factors may influence Gal-1 sensitivity to environmental conditions such as dimerization equilibrium, redox status and the availability of specific glycosylated ligands (Cerliani et al. 2017).

Within the immune system, Gal-1 is expressed in macrophages (Rabinovich et al. 1996), activated B cells (Zuñiga et al. 2001) and activated T cells (Fuertes et al. 2004). In physiologic settings, Gal-1 serves to preserve immune cell homeostasis by targeting various immune cell types in an autocrine or paracrine manner (Rabinovich et al. 2007) (Figure 1). This lectin shapes the profile of effector T cell subsets by controlling their activation, differentiation, survival and cytokine production (Sundblad et al. 2017). It controls T cell survival by interacting with glycosylated receptors, including CD45, CD43 and CD7 (Stillman et al. 2006), and by selectively deleting effector T cell populations (Rubinstein et al. 2004; Toscano et al. 2007). While cytotoxic $CD8^+$ T cells, Th1 and Th17 lymphocytes exhibit the repertoire of glycans that are essential for Gal-1 binding, Th2 lymphocytes and naive T cells display high levels of terminal α(2,6)-linked sialic acid, thus preventing the binding of this lectin (Toscano et al. 2007; Rabinovich and Toscano 2009). In addition, Gal-1 may limit T cell activation by antagonizing T cell receptor (TCR) signals (Liu et al. 2009), and inhibits T cell adhesion to ECM glycoproteins (Rabinovich, Ariel, et al. 1999a). Several studies have shown that Gal-1 triggers the expansion and recruitment of regulatory T cells (Tregs) in models of autoimmunity, pregnancy, breast cancer and parasite infection (Toscano et al. 2006; Blois et al. 2007; Dalotto-Moreno et al. 2013; Poncini et al. 2015). Furthermore, Gal-1 imprints an immunoregulatory signature in T cells, characterized by high IL-21 expression, activation of the c-Maf/aryl hydrocarbon receptor pathway and induction of IL-10 (Cedeno-Laurent et al. 2012). Moreover, with regard to the B cell compartment, Gal-1 controls the transition of activated B cells to a plasma cell phenotype (Anginot et al. 2013) and amplifies B cell activation by enhancing B cell receptor (BCR) signaling (Croci et al. 2013; Tsai et al. 2014).

The regulatory roles of Gal-1 are not limited to adaptive immunity, as it also regulates multiple events within the innate immune compartment (Figure 1). These include induction of IL-27-producing tolerogenic dendritic cells (DCs), which support the differentiation of IL-10-producing type-1 Tregs, capable of suppressing autoimmune and chronic inflammatory responses (Ilarregui et al. 2009). Furthermore, through clustering of glycans on CD43, Gal-1 inhibits immunogenic, but not tolerogenic DC tissue emigration (Thiemann et al. 2015). On the other hand, Gal-1 also promotes microglial differentiation toward an M2 phenotype that prevents inflammation-driven neurodegeneration (Starossom et al. 2012). By regulating L-arginine metabolism, Gal-1 favors the polarization of macrophages toward an M2 profile and contributes to their pro-resolving phenotype through interferon (IFN)-β-mediated mechanisms (Correa et al. 2003; Yaseen et al. 2020). Interestingly, endogenous Gal-1 differentially binds to different populations of human monocytes and macrophages in a glycan-dependent manner (Krautter et al. 2020). Furthermore, Gal-1 inhibits neutrophil recruitment to sites of inflammation and reprograms their ability to produce reactive oxygen species (Rodrigues et al. 2019; Law et al. 2020), suppresses eosinophil trafficking and survival (Ge et al. 2016) and prevents mast cell degranulation (Rabinovich et al. 2000) (Figure 1); these effects profoundly affect the development and resolution of acute and chronic inflammatory responses. Identification of different cell targets, glycosylated receptors and signaling pathways engaged by Gal-1 are paving the way for the development of novel therapeutic approaches aimed at reprogramming innate and adaptive immunity in a wide spectrum of inflammatory conditions.

In this review, we highlight both pioneer and emerging work that emphasizes the central roles of Gal-1 in chronic inflammatory conditions, particularly those involving preservation and restoration of immune cell homeostasis in several tissues and during different pathophysiologic conditions. We also discuss the therapeutic implications of these findings in cancer, autoimmune and inflammatory processes.

Cancer and inflammation

The concept that inflammation could be linked to cancer dates to 1863 when Rudolf Virchow suggested that tumors often arise at the sites of chronic inflammation (Balkwill and Mantovani 2001). Nowadays, it is well known that inflammation is an important hallmark of cancer development. Tumor-associated inflammation is

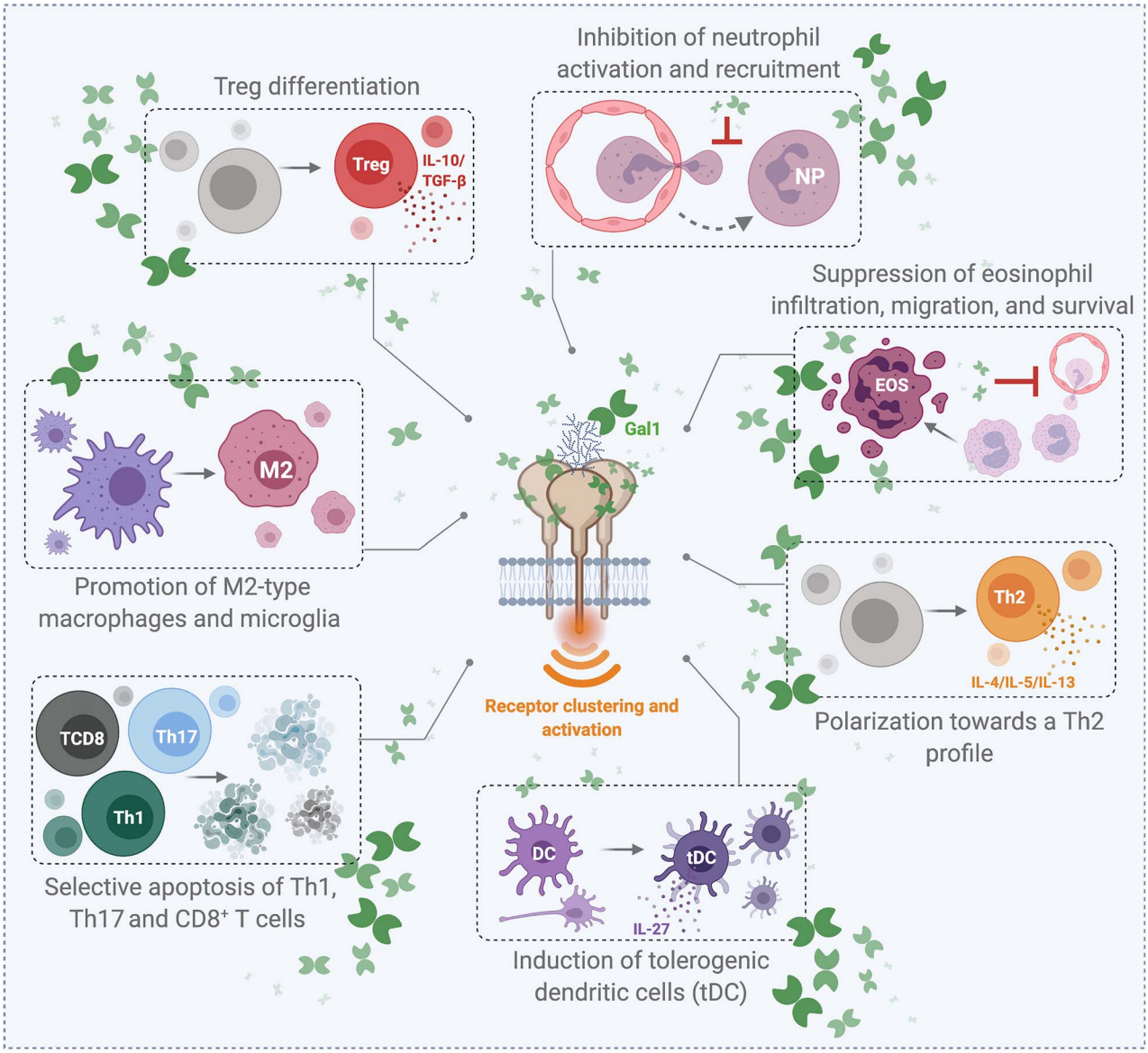

Fig. 1. Regulatory effects of Gal-1 on innate and adaptive immune cells. Galectins control inflammatory responses by modulating the fate and function of different innate and adaptive immune cells via glycosylation-dependent or -independent mechanisms. These include polarization of macrophages and microglia toward an M2 profile, expansion of Tregs, inhibition of neutrophil recruitment to sites of inflammation and production of reactive oxygen species, differentiation of T cells toward a Th2 profile, induction of tolerogenic DCs and selective deletion of Th1, Th17 and $CD8^+$ T cells. The combination of these functions may contribute to the overall effects of this lectin in chronic inflammatory disorders. Created with BioRender.com. This figure is available in black and white in print and in colour at *Glycobiology* online.

accompanied by epithelial proliferative events, neovascularization and stromal cell recruitment, all cellular processes that favor neplastic transformation (Balkwill and Mantovani 2001). However, at early stages of the disease, a controlled and suitable inflammatory response is necessary to trigger the anti-tumor immune response. During its initial phase, inflammation is central for the recruitment, differentiation and activation of lymphoid and myeloid cells (Shalapour and Karin 2019). Inflammatory events are triggered in response to external or internal insults (stress, tissue damage, infection, metabolic or genetic alterations among others) in order to promote tissue regeneration and restore homeostasis (Medzhitov 2008). The release of inflammatory cytokines and chemokines by myeloid cells boosts the immune system to eliminate the insults by activating both wound healing and epithelial cell defense programs with the ultimate goal of repairing injured tissues. After resolving the damage, the inflammatory response vanishes, returning to a homeostatic state (Mantovani et al. 2008). However, if the insult is driven by an oncogenic event and the immune response is ineffective to eliminate the disturbance, inflammation persists, leading to a chronic inflammation state (Mantovani et al. 2008). Even tumors categorized as "noninflammatory" may elicit inflammation by recruiting immune cells in order to reshape the tumor microenvironment (TME). This tumor-associated inflammatory response has a direct impact on cancer cells stimulating proliferation, inducing mutations and cell death resistance and favoring tumor growth (Greten and Grivennikov 2019). Furthermore, inflammatory mediators modulate the TME and induce

immunosuppression by recruiting myeloid-derived suppressor cells (MDSCs), Tregs, regulatory B cells (Bregs) and other immunoregulatory cell types that favor cancer progression (Greten and Grivennikov 2019).

Inflammation also influences invasion, epithelial-to-mesenchymal transition (EMT) and cell migration. Production of cytokines such as TNF and IL-1β in the TME induces EMT via activation of Twist and Slug, the key transcription factors involved in this process (Suarez-Carmona et al. 2017). In addition, MDSCs may induce the production of matrix metalloproteinases (MMPs), aiding in the remodeling of the tumor-surrounding ECM and fostering cell migration and dissemination (Greten and Grivennikov 2019). In line with these findings, MDSCs, M2 macrophages and DCs recruited to the TME can promote angiogenesis and facilitate metastasis (Shojaei et al. 2007; Sica et al. 2008).

Furthermore, cancer-related inflammation is also associated with sensitivity to different therapies, being a relevant target for the development of novel therapeutic modalities aimed at improving patient outcomes and overcoming treatment resistance (Diakos et al. 2014). However, due to the complex interactions between inflammation and anti-tumor immunity, it is of vital importance to design therapeutic alternatives that overcome immunosuppression elicited by chronic inflammation, while preserving its immunostimulatory activity (Shalapour and Karin 2019). Indeed, T cell-inflamed "hot" tumors enriched in pro-inflammatory cytokines exhibit a better response to immunotherapy. In this regard, many therapies are currently aimed to transform non-T cell-inflamed "cold" tumors into "hot" T cell-inflamed ones in order to increase the responses to immunotherapy (Shalapour and Karin 2019). Accordingly, we recently found that melanoma patients responding to anti-programmed cell death protein-1 (PD-1) or anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) treatment exhibit increased activation of the Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing 3 (NLRP3)/caspase-1/IL-1β-dependent inflammasome. Moreover, we found that therapeutic modulation of the inflammasome activation improves responses to immune checkpoint blockers in preclinical models by promoting $CD8^+$ T cell activation (Segovia et al. 2019). Thus, a more in-depth understanding of the molecular mechanisms associated with inflammation in cancer and its ability to shape anti-tumor immune responses is crucial for designing novel immunotherapeutic modalities.

Galectins play key roles in all hallmarks of cancer, including promotion of inflammation and evasion of immune responses (Girotti et al. 2020). We and others have demonstrated that Gal-1 has anti-inflammatory and pro-resolving activities by targeting multiple immune cell types. In this context, Gal-1 secreted by human and mouse melanoma cells thwarts anti-tumor T cell responses. Accordingly, Gal-1 knockdown in the B16 melanoma mouse model suppresses tumor growth by unleashing Th1 and cytotoxic $CD8^+$ T cells, thus promoting an effective anti-tumor T cell response (Rubinstein et al. 2004). Accordingly, Holst et al. have recently shown that high levels of intratumoral Gal-1 are associated with low frequency of cytotoxic $CD8^+$ T cells in the TME and with poor clinical outcomes in a subgroup of peripheral T cell lymphomas (Holst et al. 2020). The mechanism underlying these events involves, at least in part, the ability of Gal-1 to induce selective apoptosis of Th1, Th17 and $CD8^+$ T lymphocytes via interaction with specific glycosylated ligands on the surface of these cells (Rubinstein et al. 2004; Toscano et al. 2007). In this regard, high levels of Gal-1 in different TMEs may favor the polarization of T cells toward a Th2 phenotype, defined as pro-tumorigenic in the context of an antitumor immune response. For instance, the upregulation of Gal-1 in Reed Sternberg cells by the Epstein–Barr virus can elicit a Th2-skewed immunosuppressive microenvironment, which is typical of classical Hodgkin's lymphoma (Juszczynski et al. 2007). In this context, Gal-1 has been identified as a biomarker of refractory disease in patients with this hematological malignancy (Kamper et al. 2011). Moreover, further studies have substantiated the role of Gal-1 in the development and maintenance of immune evasive programs triggered by a myriad of different tumor types, including melanoma, head and neck squamous cell carcinoma (HNSCC), neuroblastoma, glioblastoma, ovary, pancreatic, prostate and breast adenocarcinomas (Rabinovich and Conejo-Garcia 2016). With regard to breast cancer, silencing of tumor-derived Gal-1 in a triple-negative breast cancer mouse model leads to reduced tumor burden and metastasis formation, effects that were accompanied by lower infiltration of $Foxp3^+$ Tregs within the tumor, tumor-draining lymph nodes, spleen and metastatic sites (Dalotto-Moreno et al. 2013). Furthermore, Gal-1 secreted by HNSCC has been shown to remodel the tumor endothelium inducing expression of PD-L1 and Gal-9, thus preventing transendothelial T cell migration into the tumor and modulating responses to anti-PD-1 immunotherapy (Nambiar et al. 2019). Thus, Gal-1 fosters an immunosuppressive microenvironment, either locally or systemically, thwarting the development of an effective anti-tumor immune response.

The regulatory role of Gal-1 also impacts in the innate branch of the anti-tumor immune response. In a high-grade glioma mouse model (GL261), Gal-1 promotes the recruitment and migration of MDSCs as well as tumor-associated macrophages (TAMs) into the TME. Moreover, in this glioma mouse model, silencing of tumor-derived Gal-1 prolonged the survival of tumor-bearing mice (Verschuere et al. 2014). Moreover, glioma-derived Gal-1 polarizes $Gr\text{-}1^+CD11b^+$ myeloid cells toward an immunosuppressive phenotype, thus supporting tumor progression. Therefore, targeting Gal-1 in central nervous system (CNS) tumors, which are highly resistant to immunotherapy, could be a promising therapeutic strategy by reprogramming the inflammatory microenvironment in the brain, allowing recruitment of inflammatory monocytes and subsequent tumor eradication by natural killer (NK) cells (Baker et al. 2016). In this context, we found that Gal-1 limits the immunogenic activity of DCs in a murine melanoma model. This lectin stimulates the differentiation of tolerogenic DCs, fostering an immunosuppressive TME and compromising the development of effector anti-tumor T cell responses (Ilarregui et al. 2009). Supporting the broad immunosuppressive activity of Gal-1, its expression has been intimately linked to CD163, a marker of M2 macrophages, in classical Hodgkin's lymphoma and multiple myeloma (Kamper et al. 2011; Andersen et al. 2017). The underlying mechanisms implicated in this polarizing capacity involve the modulation of L-arginine metabolism, major histocompatibility complex (MHC)-II-dependent antigen presentation, Fcγ receptor I-dependent phagocytosis and IFN-β-regulated pathways (Correa et al. 2003; Barrionuevo et al. 2007; Starossom et al. 2012; Yaseen et al. 2020).

In addition to its role in regulating tumor-immune evasion, Gal-1 expression has been implicated in the progression from chronic inflammation to cancer development as occurs in liver and pancreatic cancer models (Tang et al. 2014; Tang et al. 2018; Potikha et al. 2019). Interestingly, Gal-1 expression protected from tumor initiation in a mouse model of hepatocellular carcinoma (HCC) mediated by chronic liver inflammation (CLI). Gal-1 deficiency in this mouse model enhances CLI, resulting in fibrosis, tissue injury, cell proliferation and immune cell infiltration (Potikha et al. 2019). However,

at advanced stages of HCC, Gal-1 displayed mainly pro-tumorigenic functions and its expression correlated with poor patient prognosis. Consistently, knocking down Gal-1 in HCC tumors resulted in significantly slower tumor growth rate, and administration of the Gal-1 inhibitor, OTX008, in tumor-bearing mice reduced tumor proliferation (Leung et al. 2019). Remarkably, Gal-1 expression correlated with tumor progression (Laderach et al. 2013; Rabinovich and Conejo-García 2016; Orozco et al. 2018) and poor prognosis (Jung et al. 2007; Chiang et al. 2008) in a myriad of different cancer types. Of note, expression of Gal-1 by stromal cells such as cancer-associated fibroblasts (CAFs) or by tumor cells, regulates the expression of genes associated with migration and invasion, including MMP-2 and -9 as well as β_1-integrin, and promotes EMT by activating different transcription factors in oral squamous cell carcinoma (OSCC) (Wu et al. 2009), gastric (He et al. 2014) and pancreatic cancer (Tang et al. 2017; Orozco et al. 2018). Accordingly, in a KRAS-driven pancreatic adenocarcinoma model, Gal-1 controlled inflammation and angiogenesis through paracrine and autocrine pathways. Genetic ablation of Gal-1 gene (*Lgals1*) in a model of pancreatic cancer enhanced the survival of tumor-bearing mice and diminished tumor-driven inflammation and metastasis (Orozco et al. 2018).

As mentioned above, tumor-derived Gal-1 showed a relevant role in the generation of tumor-associated blood vessels necessary for tumor growth and metastasis (Thijssen et al. 2010). In particular, hypoxic conditions as well as inflammatory cytokines upregulate the expression of Gal-1 by tumor cells (Croci et al. 2012) and induce significant changes in the glycosylation signature of the vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2). This effect increases the endothelial cell (EC) sensitivity to Gal-1 binding and subsequent activation of pro-angiogenic programs (Croci et al. 2014). Targeting the Gal-1-glycan axis sensitized refractory tumors to anti-VEGF treatment by preventing the activation of compensatory mechanisms. Antibody-mediated Gal-1 blockade promoted vessel normalization and enhanced immune cell infiltration in the TME, particularly IFN-γ-producing CD8$^+$ T cells (Croci et al. 2014). Furthermore, Gal-1 produced by $\gamma\delta$-T lymphocytes in the TME accelerated malignant progression by linking commensal microbiota, tumor-promoting inflammation and immunosuppression (Rutkowski et al. 2015). Thus, Gal-1 connects cancer-related inflammation, anti-tumor immunity and tumorigenesis.

In addition to the extracellular functions of Gal-1, intracellularly, this lectin sustains proliferative signals via specific interactions with the oncogenic driver gene RAS (Paz et al. 2001). The association of Gal-1 with RAS in lung cancer promotes chemoresistance and tumor progression through the upregulation of inflammatory signals, including cyclooxygenase-2, p38 and extracellular regulated kinase (ERK) pathways (Chung et al. 2012). Particularly, Huang et al. proposed that extracellular stimuli induce Gal-1 expression in renal cancer cells as well as RAS activation, thus enhancing Gal-1/RAS interactions and the expression of CXCR4, with critical implications in EMT, inflammation and angiogenesis (Huang et al. 2014).

In conclusion, Gal-1 is an active player in the modulation of the inflammatory response in cancer. Gal-1 can engage glycosylated cell surface receptors, oncogenic proteins, transcription factors or cell adhesion molecules and can trigger distinct signaling pathways that activate inflammation-related programs, thus influencing the metastatic properties of both primary tumors and early disseminated cancer cells (Figure 2). Thus, Gal-1 emerges as a glycocheckpoint that controls cancer-driven inflammation and neoplastic progression, highlighting its role as a promising therapeutic target at different stages of cancer evolution (Girotti et al. 2020).

CNS inflammation

Multiple sclerosis (MS) is a demyelinating autoimmune and inflammatory disease of the CNS that leads to neurological symptoms and progressive disability (Stys et al. 2012). Further understanding of the pathogenesis of this chronic inflammatory disease in its different forms (relapsing–remitting, primary progressive or secondary progressive) is needed in order to identify potential disease targets and design novel therapeutic strategies. Several studies have been conducted to understand the role of galectins in CNS inflammation (Stancic et al. 2011; Mendez-Huergo et al. 2014). In this context, a significant increase in Gal-1 expression was detected in *postmortem* lesions, particularly in cultured astrocytes from MS patients (Stancic et al. 2011). The role of Gal-1 in CNS inflammation was explored in experimental autoimmune encephalomyelitis (EAE), an animal model that recapitulates some of the immunological and clinical manifestations of MS. This includes the increased frequency of Th17 and Th1 cells at the early and late stages of CNS inflammation (Mendez-Huergo et al. 2014). The demonstration that Gal-1 binds to specific glycans on the cell surfaces of Th1 and Th17 pathogenic cells and controls the execution of cell death programs, prompted us to explore the role of this lectin in neuroinflammation (Toscano et al. 2007). Consistent with the immunosuppressive activity of endogenous Gal-1, *Lgals1*$^{-/-}$ mice exhibited increased inflammation and demyelination areas in spinal cord sections and displayed greater disease severity compared to WT mice when immunized with myelin oligodendrocyte glycoprotein (MOG)35–55. Importantly, exacerbation of EAE in *Lgals1*$^{-/-}$mice was associated with an increased frequency of antigen-specific Th17 and Th1 cells. Consistently, treatment of EAE mice with recombinant Gal-1 (rGal-1) decreased antigen-specific IL-17- and IFN-γ-producing CD4$^+$ T cells. These results showed that Gal-1 induces selective deletion of antigen-specific Th17 and Th1 cells, limiting their frequency in vivo and attenuating the severity of this demyelinating disease (Toscano et al. 2007). These results provide a rational explanation for early findings demonstrating the immunomodulatory effects of Gal-1, originally purified as a placental β-galactoside-binding protein, in CNS inflammation (Offner et al. 1990) and the effects of electrolectin in a model of myasthenia gravis in rabbits (Levi et al. 1983).

The ability of Gal-1 to induce IL-27-producing tolerogenic DCs (Ilarregui et al. 2009) prompted us to validate this immunoregulatory activity in vivo. Mice immunized with (MOG)35-55 peptide and further treated with (MOG)35-55-pulsed DCs preexposed to Gal-1 exhibited lower disease severity than mice treated with (MOG)35-55-pulsed control DCs. Furthermore, DCs purified from WT, EAE mice adoptively transferred to EAE *Lgals1*$^{-/-}$mice contributed to the resolution of autoimmune neuroinflammation (Ilarregui et al. 2009). Consistently, WT mice had increased numbers of Tr1 and Foxp3$^+$ Tregs in the CNS and periphery than *Lgals1*$^{-/-}$mice during the course of EAE (Mari et al. 2016). These findings provide a rational explanation for early observations demonstrating the presence of anti-Gal-1 autoantibodies in plasma from MS patients (Lutomski et al. 1997), suggesting that blockade of this lectin may contribute to the pathogenesis of CNS inflammation.

Gal-1 was also identified as a key regulator of microglial activation. In particular, Gal-1 interactions with core-2 *O*-glycans on CD45 phosphatase promoted de-activation of M1 microglia

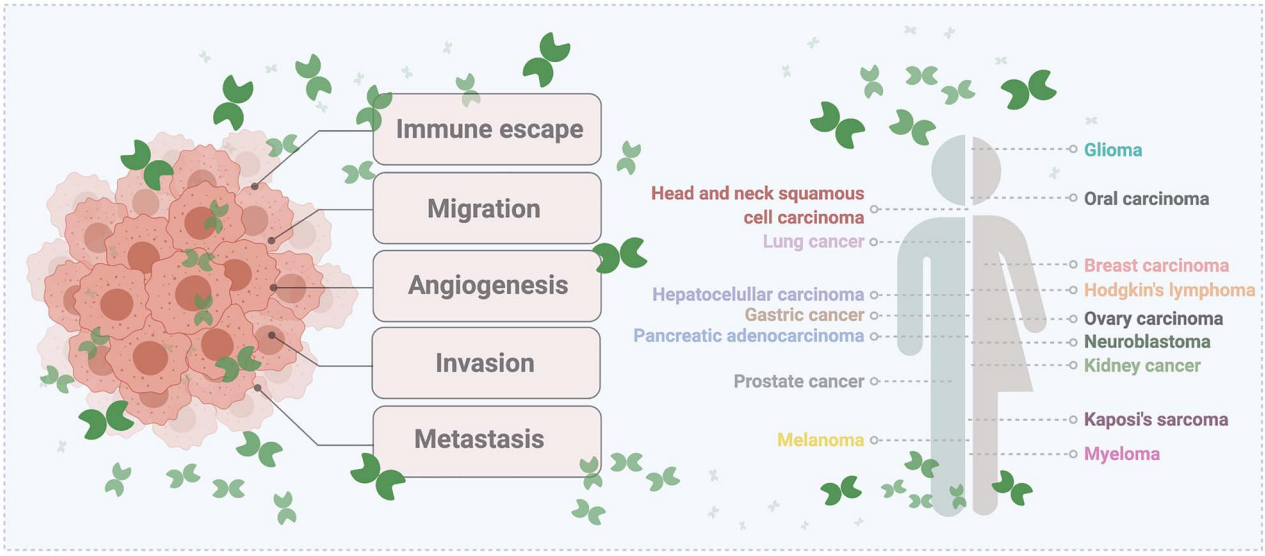

Fig. 2. Gal-1 acts as an "on–off" switch that controls different events during cancer progression. Several events lead to tumor growth and progression, including promotion of inflammatory responses and immune evasion mechanisms. Gal-1 links tumor-promoting inflammation and immunosuppression in different tumor settings. Created with BioRender.com. This figure is available in black and white in print and in colour at *Glycobiology* online.

by reducing nitric oxide (NO) synthesis, lowering expression of pro-inflammatory cytokines and polarizing these cells toward an M2-type profile, leading to neuroprotection. In the EAE model, treatment with rGal-1 attenuated disease severity through microglia deactivation (Starossom et al. 2012). Supporting these findings, Mahajan and collaborators demonstrated that Gal-1 treatment induced modulation of L-arginine pathway, by rewiring the balance of NO and arginase in microglia, indicating a possible role of Gal-1 in neurocognitive disorders associated with human immunodeficiency virus (HIV) infection (Aalinkeel et al. 2017). These results are consistent with our previous findings showing a regulatory role of Gal-1 in the control of L-arginine metabolism in activated peritoneal macrophages (Correa et al. 2003). Remarkably, in an experimental model of demyelination induced by lysolecithin, rGal-1 administration decreased demyelinated areas, induced remyelination and attenuated the response of oligodendroglial precursor cells (Rinaldi et al. 2016). In line with these findings, Gal-1, mainly in its dimeric form, promoted the functional recovery of spinal lesions by interfering with the inhibitory signals triggered by Semaphorin 3A binding to neuropilin-1/plexinA4 complex, supporting the use of this lectin for the treatment of spinal cord injury patients (Quintá et al. 2014). Whether Gal-1-driven regulation of the inflammatory response contributes to this neuroprotective effect still remains uncertain. Thus, Gal-1 controls several regulatory circuits mediated by effector T cells, DCs, microglia, neurons and oligodendrocytes within the CNS to limit the severity of inflammation and neurodegeneration.

Salivary gland inflammation

Sjögren's syndrome is a chronic autoimmune disease characterized by the lymphocytic infiltration of exocrine salivary and lacrimal glands and by the presence of a wide range of autoantibodies (Mavragani and Moutsopoulos 2020). Recently, we found spontaneous salivary gland autoimmunity in aged mice lacking Gal-1 or devoid of β1,6*N*-acetylglucosaminyltransferase 5 (Mgat5), a glycosyltransferase responsible for generating β1,6-branched complex *N*-glycans, which serve as a limiting step for LacNAc extension and Gal-1 binding (Martínez-Allo et al. 2020). This sialadenitis phenotype recapitulates the clinical and histopathologic manifestations of human Sjögren's syndrome. These include increased frequency of antinuclear autoantibodies and elevated frequencies of $CD45^+$ cells and $CD8^+$ T cells in aged *Lgals1*$^{-/-}$ compared WT mice. Furthermore, *Lgals1*$^{-/-}$ aged mice displayed enhanced T cell activation and recruitment to salivary glands, characterized by greater number of IFN-γ-producing PD-$L1^+$ $CD8^+$ T cells. Moreover, Gal-1-deficient $CD11c^+$ DCs displayed increased immunogenic capacity and lower potential to promote Treg cell differentiation. The effect of endogenous Gal-1 was studied by analyzing nonobese diabetic (NOD) mice, a well-established mouse model of Sjögren's syndrome. The results showed that endogenous Gal-1 decreased with age in the serum and salivary glands, leading to a pronounced autoimmune phenotype that could be rescued by rGal-1 administration (Martínez-Allo et al. 2020). Altogether, these findings provide a definitive proof-of-concept that endogenous Gal-1 hierarchically regulates immune tolerance in vivo and acts as a safeguard mechanism to prevent age-dependent spontaneous autoimmunity.

Pancreatic inflammation

Type I diabetes (T1D) is an autoimmune disease where insulin-producing pancreatic β-cells are destroyed by pathogenic, activated T cells. Transgenic bone marrow-derived DCs expressing Gal-1 delayed the development of T1D in a mouse model of diabetes, where immunodeficient NOD mice (NOD*rag1*$^{-/-}$) were transferred with splenocytes from female diabetic NOD mice (Perone et al. 2006). This protective effect was associated with a decreased number of IFN-γ-secreting, antigen-specific $CD4^+$ T cells and increased levels of T cell apoptosis (Perone et al. 2006). However, the prevention of diabetes induction was limited, and all mice developed the disease at some point. To advance a step further, Perone et al. studied the direct administration of rGal-1 in NOD mice, which caused a reduction of the Th1 phenotype by shifting the balance toward Th2 and Treg cell responses, suppressing the occurrence of pathogenic pancreatic β

cells and preventing hyperglycemia (Perone et al. 2009). Accordingly, Gomez-Touriño et al. showed lower levels of Gal-1 secretion by peripheral blood mononuclear cells in T1D patients compared to healthy donors, mainly caused by a decrease in Gal-1 synthesis by monocytes (Gómez-Touriño et al. 2011). Further studies should focus on dissecting the role of Gal-1 in the regulation of glucose metabolism and insulin resistance.

Chronic pancreatitis (CP), is a multifactorial disease that is characterized by exocrine and endocrine dysfunction, caused by severe inflammation and fibrosis (Xue et al. 2015). Tang et al. found gradually increasing Gal-1 expression in normal pancreas, CP and pancreatic cancer (Tang et al. 2014). In particular, patients with CP showed increased *LGALS1* messenger RNA (mRNA) expression in pancreatic fibroblasts (pancreatic stellate cells [PSCs]) and pancreatic nerves compared to healthy control individuals (Wang et al. 2000). Accordingly, Gal-1 was similarly overexpressed between CP and activated PSCs compared to the normal pancreas and undifferentiated PSCs, and this effect was related to an increase in the migratory and proliferative capacity of PSCs (Tang et al. 2018). In this regard, exogenous Gal-1 increased not only PSC proliferation but also collagen synthesis, and this effect was found to be glycan-dependent (Fitzner et al. 2005). Consistently, Gal-1 activated signaling pathways that were mediated by ERK, JNK, activating protein-1 (AP-1) and nuclear factor Kappa B (NF-κB) in PSCs (Masamune et al. 2006). Altogether, these findings underpin the critical role of Gal-1 in the progression from CP to pancreatic cancer.

Ocular inflammation

Intraocular inflammatory diseases can severely impair vision, eventually leading to blindness (Caspi 2010). Autoimmune uveitis is an inflammatory process of uveal components due to an autoimmune reaction to self-antigens, which may occur as an isolated entity or associated with a systemic autoimmune disease. Given its proximity to other areas of the eye, inflammation can cause damage to the retina, vitreous body and optic nerve (Caspi 2010). Analysis of the plasma from uveitis patients revealed increased levels of immunoglobulin G (IgG) and immunoglobulin E (IgE) anti-Gal-1 autoantibodies, which correlated with the severity and clinical parameters of the disease (Romero et al. 2006).

Uveitis can be studied experimentally in different rodent models: the mouse model of experimental autoimmune uveitis (EAU) is induced by the immunization of mice with retinal antigens, including the interphotoreceptor retinoid-binding protein (Caspi 2010), whereas an alternative model is induced by the administration of endotoxins like lipopolysaccharides (LPS) in rats (Zanon et al. 2015). Studies carried out in both models showed that the administration of rGal-1 attenuates the severity of autoimmune ocular inflammation (Toscano et al. 2006; Zanon et al. 2015). In particular, treatment of EAU with rGal-1 reduced the infiltration of immune cells, promoted T cell apoptosis and suppressed Th1 cells, tilting the balance toward Th2 and Treg cell responses (Toscano et al. 2006). This immunoregulatory activity involved an increase in transforming growth factor (TGF)-β_1 and IL-10 production. Moreover, adoptive transfer of $CD4^+$ T cells from rGal-1-treated mice ameliorated the disease severity in naive receptors with EAU (Toscano et al. 2006). Furthermore, in endotoxin-induced uveitis, the administration of rGal-1 reduced the infiltration of neutrophils in the eye by modulating L-selectin and β_2-integrin and by decreasing the expression of pro-inflammatory cytokines, such as IL-6, IL-1β and monocyte chemotactic protein-1 (MCP-1) (Zanon et al. 2015). These findings support the potential therapeutic use of rGal-1 for the treatment of ocular inflammatory disorders by modulating innate and adaptive immune programs.

Allergic conjunctivitis (AC) is caused by an immune response to allergens and is characterized by the inflammation of the conjunctiva caused by IgE-dependent or -independent hypersensitivity reactions (Friedlaender 2011). Mello-Bosnic et al. (2015) found in the experimental model of OVA-induced AC that rGal-1 administration attenuated disease symptoms, IgE levels and Th2-type cytokines, such as IL-4 and IL-13 in draining lymph nodes. Furthermore, rGal-1 treatment controlled β_2-integrin expression in neutrophils and eosinophils, although no effect was found on eosinophil activation.

Eye infections can cause various inflammatory lesions and even blindness. For example, herpes simplex virus (HSV) infection causes complications such as stromal keratitis, which is primarily driven by Th1 and Th17 inflammatory responses (Suryawanshi et al. 2013). Rajasagi and colleagues showed that *Lgals1*$^{-/-}$mice had greater disease severity compared to their WT counterparts after ocular infection with HSV and that treatment with rGal-1 reduced complications of experimental keratitis (Rajasagi et al. 2012). Mechanistically, rGal-1 administration induced a reduction of pro-inflammatory cytokines including IFN-γ and IL-17, a rise of anti-inflammatory cytokines, such as IL-10, and downmodulation of corneal neutrophil infiltration as a consequence of lower chemokine production (Rajasagi et al. 2012). Moreover, the immunomodulatory effects of Gal-1 were assessed during corneal infection by *Pseudomonas aeruginosa*. Suryawashi et al. found that subconjunctival injections of rGal-1 suppressed keratitis in *P. aeruginosa*-induced corneal immunopathology, reduced corneal immune cell infiltration, blunted Th17 pro-inflammatory responses and promoted Th2- and IL-10-mediated anti-inflammatory responses (Suryawanshi et al. 2013). Thus, Gal-1 dampens ocular inflammation caused by autoimmune, allergic or infectious insults by shaping both innate and adaptive immune compartments.

Intestinal inflammation

Inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, are characterized by dysregulation of intestinal homeostasis due to different mechanisms involving enhanced pathogenic T cell responses and decreased tolerance to commensal microbiota (Sartor 2006). Recently, Yu et al. showed that serum Gal-1 levels are higher in IBD patients as compared to healthy individuals and, although not correlated with disease activity, it was proposed that serum Gal-1 could potentially be used as a diagnostic biomarker in combination with other clinical parameters (Yu et al. 2020). Moreover, expression of Gal-1 (as well as Gal-3, -4 and -9) was found to be dysregulated in the inflamed tissues of IBD patients compared with noninflamed IBD or control samples (Papa Gobbi et al. 2016). In early studies, we demonstrated the therapeutic and prophylactic roles of Gal-1. Administration of rGal-1 suppressed 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice by increasing the susceptibility of activated T cells of the lamina propria to antigen-induced apoptosis and by reducing Th1 responses in the colon (Santucci et al. 2003). Also, early administration of this lectin lowered the number of activated T cells in the spleen, reduced TNF, IL-1β, IL-12 and IFN-γ in the colonic mucosa and suppressed the production of IFN-γ-producing $CD4^+$ T cells (Santucci et al. 2003). Of note, pro-inflammatory cytokines induced increased binding of Gal-1 to intestinal epithelial cells (IECs) (Muglia et al. 2016), suggesting that inflammation may foster Gal-1-glycan

interactions. In this regard, a dose-dependent effect of Gal-1 has been described; whereas low Gal-1 levels favored tolerogenic intestinal responses, high levels of this lectin modulated the viability of IECs via caspase-dependent pathways (Muglia et al. 2016). Further studies should be aimed at examining the regulatory effects of endogenous Gal-1–glycan interactions in IBD.

In patients with celiac disease, an intestinal inflammatory response associated with a dysregulated reaction to wheat gluten peptides occurs. Gal-1 was poorly expressed in the epithelium and stroma of celiac disease patients compared to intestinal tissue from normal individuals (Sundblad et al. 2018). Surprisingly, increased expression of Gal-1 was found in the interstitium of recovered villi from patients' duodenal biopsies following a lifelong gluten-free diet. Intense Gal-1 staining was also found in fibroblasts, macrophages and a group of lymphocytes, although epithelial cells showed weaker staining. Increased Gal-1 expression positively correlated with the number of $Foxp3^{+}$ cells, suggesting a key role for Gal-1 in the restoration of epithelial gut homeostasis after adherence of celiac disease patients to gluten-free diet (Sundblad et al. 2018). Although these associations need further clinical and experimental validations, these results suggest the potential role of Gal-1 as a biomarker for monitoring gluten-free diets in patients with celiac disease.

As shown in IBD, in food allergy models, pro-inflammatory responses could also regulate the binding of Gal-1 to the IECs (Muglia et al. 2016). In particular, Yang et al. studied the role of Gal-1 in a food allergy model, induced by ovalbumin challenge. Administration of rGal-1 inhibited allergic responses by suppressing mast cell activation through binding to IgE/FcεRI (Yang et al. 2018), highlighting the potential of Gal-1 in controlling allergic inflammation.

Inflammation in the female reproductive tract

Among the most common inflammatory disorders in the female reproductive tract are those caused by infections, such as the bacteria *Chlamydia trachomatis* (Ct). Since Ct is an obligate intracellular pathogen, bacterial internalization is a priority for establishing infection. By recognizing complex *N*-glycans, Gal-1 binds to the surface of both Ct and human cervical epithelial cells and controls bacterial infection. Exposure to Gal-1 significantly increased Ct adhesion and entry to Hela cells in a glycan-dependent manner. This effect was physiologically relevant since endogenous Gal-1 or its glycosylated ligands controlled Ct infection in an experimental model in vivo, as shown in *Lgals1*$^{-/-}$ and *Mgat5*$^{-/-}$ mice (Lujan et al. 2018). Hence, targeting the Gal-1-*N*-glycan axis emerges as a promising therapeutic approach for preventing or attenuating Ct infection.

Trichomoniasis is a sexually transmitted infection caused by the parasite *Trichomonas vaginalis*. Given that *T. vaginalis* is an extracellular parasite, it requires the adhesion to cell surface receptors to establish and maintain infection. Particularly, the lipophosphoglycan (LPG), anchored to the parasite surface, has a critical role in host cell adherence, inflammation and invasion. Okumura and colleagues found that Gal-1 expressed by cervical epithelial cells binds to the LPG on *T. vaginalis* in a carbohydrate-dependent manner, facilitating infection (Okumura et al. 2008).

HSV-1 is becoming an increasing cause of genital infections and inflammation, which is still underappreciated. Expression of Gal-1 is dramatically upregulated in Vero cell cultures infected with HSV-1, and supernatants from HSV-1-infected cells induced the apoptosis of activated T cells in a Gal-1-driven and glycan-dependent fashion (Gonzalez et al. 2005). Since apoptosis of cytotoxic T cells contributes to immune evasion mechanisms triggered by HSV-1, targeting Gal-1 emerges as a potential therapeutic strategy in HSV-1 infections and associated inflammatory responses.

Likewise, Gal-1 has been shown to affect HIV-1 infection through direct interaction of CD4 receptor with complex glycans on gp120 (Sato et al. 2012), although the role of this lectin in HIV-associated inflammatory responses remain to be elucidated.

Endometriosis is a gynecological disorder defined by the presence of ectopic endometrial tissue implanted as functional lesions outside of the uterus, causing severe pelvic pain, inflammation and infertility. Although the precise etiopathogenic mechanisms leading to the occurrence of endometriosis remain elusive, angiogenesis and inflammation are particularly dysregulated, thus mirroring the TME (Bastón et al. 2014). Given the involvement of Gal-1 in reproductive disorders (Blidner and Rabinovich 2013) and tumor angiogenesis (Croci et al. 2012; Croci et al. 2014), we investigated the contribution of this lectin to development of endometriotic lesions. Gal-1 was highly elevated in endometriotic and eutopic endometrial stromal cells and ECs but was absent in both endometriotic and eutopic endometrial epithelial cells (Bastón et al. 2014). In an experimental model, lack of endogenous Gal-1 resulted in decreased number and size of endometriotic lesions and their vascular areas through mechanisms that were independent of VEGF. Accordingly, blockade of Gal-1 resulted in a reduction of the mean size of the lesions and their vascularized areas, highlighting the potential role of this lectin as a therapeutic target in endometriosis. Collectively, these data underscore the relevance of Gal-1 during inflammatory responses associated with infections and noninfectious disorders in the female reproductive tract.

Inflammation in the male reproductive tract

In the testis, another immune privileged site, Gal-1 expression is abundant in Leydig cells, seminiferous tubules, Sertoli cells and normal mouse germ cells (Dettin et al. 2003; Pérez et al. 2015). The role of Gal-1 in the inflammation of the male reproductive tract was investigated in autoimmune orchitis, an inflammatory testicular disease, characterized by the presence of specific anti-sperm antibodies that can cause spermatozoa and spermatids apoptosis, often resulting in infertility. Given the abundant expression of Gal-1 in the testis (Dettin et al. 2003) and the induction of tolerogenic DCs by Sertoli-derived Gal-1 (Gao et al. 2016), we explored the role of this lectin in orchitis, an experimental model of testicular autoimmune inflammation. Strikingly, expression of Gal-1 did not correlate with disease severity. Moreover, in contrast to other autoimmune inflammatory disorders, *Lgals1*$^{-/-}$ mice had less severe disease than control mice (Pérez et al. 2015). However, administration of rGal-1 mice with orchitis suppressed testicular inflammation (Pérez et al. 2015). Adding complexity to these findings, Lei et al. showed that treatment with both rGal-1 and TNF synergistically increased the inflammatory response in mice with orchitis (Lei et al. 2018). Whether the different effects of endogenous versus exogenous Gal-1 in testis inflammation, as compared to other models, could be associated to the nature of this immune privileged tissue, accompanying cytokines or differential modulation of early or late inflammatory responses, still remains to be explored. Nevertheless, these results support the idea of a dual role of Gal-1 in the control of testicular inflammation.

Pregnancy-associated inflammatory disorders

The pivotal role of Gal-1 in the maintenance of tolerogenic circuits and preventing inflammatory responses during pregnancy has been

well documented (Blidner and Rabinovich 2013; Barrientos et al. 2014). During gestation, high amounts of Gal-1 are produced by the maternal decidua, the placenta and the embryo (Iglesias et al. 1998; von Wolff et al. 2005; Ramhorst et al. 2012; Tirado-González et al. 2013). The mechanisms underlying the physiological functions of Gal-1 at the fetomaternal interface have been elucidated in a mouse model of stress-induced fetal loss. Interestingly, administration of rGal-1 restored cytokine balance through induction of tolerogenic DCs and subsequent expansion of Tregs, thus preventing fetal rejection (Blois et al. 2007). Accordingly, mice lacking Gal-1 were more susceptible to stress-induced fetal loss in allogeneic matings compared to their WT counterpart (Blois et al. 2007). Supporting these findings, rGal-1 inhibited LPS-induced IL-6 production by decidual cells in vitro (Gómez-Chávez et al. 2015). As expected from its central role in tolerance induction, dysregulation of Gal-1 expression during pregnancy has been implicated in several reproductive disorders. In women with spontaneous recurrent abortion, Gal-1 expression was decreased in the placental villous tissue and sera compared to normal pregnancies (Liu et al. 2006; Ramhorst et al. 2012; Tirado–González et al. 2013). Moreover, these patients showed an increased frequency of anti-Gal-1 autoantibodies compared to women with two or more successful pregnancies (Ramhorst et al. 2012). These findings emphasize the pivotal role of Gal-1 in attenuating potentially harmful maternal immune responses. Interestingly, a single nucleotide polymorphism of the *LGALS1* gene was associated with the development of gestational diabetes mellitus, the most common pregnancy-related inflammatory syndrome that is associated with adverse maternal and fetal outcomes (Blois et al. 2014). Thus, Gal-1 functions as a safeguard mechanism that controls adverse inflammatory responses during pregnancy.

Kidney inflammation

Inflammation of the kidney, a condition called nephritis, comprises a variety of entities caused by infections, autoimmune disorders and toxins. Although Gal-8 and Gal-9 have been demonstrated to have renoprotective effects, the role of Gal-1 in kidney injury is uncertain (Gu et al. 2020). Recent studies demonstrated that progression of kidney function decline is associated with increased circulating Gal-1 levels (Kuo et al. 2020). In a rat model of ischemia–reperfusion injury, pretreatment with rGal-1 attenuated renal parameters, with the recovery of renal function, protecting against influx of leukocytes, cell death and oxidative stress (Carlos et al. 2018). Moreover, rGal-1 injection prolonged survival, reduced IFN-γ production and $CD8^+$ T cell-mediated cytotoxicity in an allogeneic renal transplantation model (Xu et al. 2010). Finally, Gal-1 ameliorated nephrotoxic serum nephritis in Wistar Kyoto rats by inhibiting the accumulation of macrophages in renal glomeruli (Tsuchiyama et al. 2000). Thus, Gal-1 displays renal protective effects by reducing innate and adaptive inflammatory responses.

Lung inflammation

In terms of the lung, both nonspecific and antigen-specific immune mechanisms may lead to an inflammatory response. While this response is usually protective and beneficial, airway inflammation also has the potential to cause injury, particularly in asthmatic patients. In a model of asthma, Gal-1 limited eosinophil recruitment to allergic airways and suppressed airway inflammation by inhibiting leukocyte migration and promoting eosinophil apoptosis (Ge et al. 2016). In vivo, allergen-challenged mice lacking Gal-1 exhibited increased recruitment of eosinophils and $CD3^+$ T cells to the lung as well as elevated peripheral blood eosinophils relative to WT mice. Further, these animals had increased susceptibility to airway hyperresponsiveness and displayed elevated levels of TNF in lung tissue (Ge et al. 2016). Furthermore, treatment with rGal-1 suppressed IL-25, but not IL-33 nor thymic stromal lymphopoietin, in the affected lungs (Lv et al. 2019). Interestingly, low levels of Gal-1 were found in macrophages from the sputum samples of asthmatic patients (Sanchez-Cuellar et al. 2012). Thus, Gal-1 controls airway inflammation by modulating the fitness of eosinophils, T cells and macrophages.

Osteoarticular inflammation

Rheumatoid arthritis (RA) is a chronic multifactorial disease characterized by the infiltration of immune cells, including lymphocytes, macrophages and plasma cells, to the synovial membrane leading to irreversible joint damage. Current treatment options consist of blocking pro-inflammatory cytokines or modulating T cell activation. The potential of Gal-1 as a biomarker was studied in the tissue, serum and synovial fluid of arthritis patients. Immunohistochemical analysis revealed downregulation of Gal-1 expression in synovial tissue from patients with juvenile idiopathic arthritis (Harjacek et al. 2001). Moreover, lower levels of Gal-1 were detected in the synovial fluid from RA patients (Xibillé-Friedmann et al. 2013), whereas increased concentrations of this lectin were found in the sera from RA patients compared to healthy individuals, correlating with the severity of the disease (Mendez-Huergo et al. 2019). These findings were recently confirmed in sera, but not in synovial fluid, from an independent cohort of patients (Triguero-Martínez et al. 2020).

The therapeutic role of Gal-1 in RA was studied in the collagen-induced arthritis (CIA) model. Administration of Gal-1 or synovial fibroblasts engineered to secrete Gal-1 ameliorated joint inflammation and disease progression (Rabinovich, Daly, et al. 1999b). Daily rGal-1 treatment resulted in a reduction of anti-collagen type-II IgG levels and a shift toward a Th2-dominant anti-inflammatory response, characterized by increased amounts of IL-5 and decreased IFN-γ production (Rabinovich, Daly, et al. 1999b). Moreover, Wang and colleagues found broad anti-inflammatory activity in arthritic rats treated with lentiviral vectors overexpressing Gal-1 (Wang et al. 2010). Furthermore, *Lgals1*$^{-/-}$ mice evidenced a more severe inflammatory response in the CIA model with higher penetrance and an accelerated clinical onset and elevated pro-inflammatory cytokines, such as IL-17 and IL-22 (Iqbal et al. 2013), thus underscoring the role of endogenous Gal-1 in joint inflammation.

Finally, in a model of osteoarthritis, a prevalent joint disease characterized by cartilage destruction, Gal-1 expression in articular chondrocytes correlated with disease activity. Particularly, in this model, Gal-1 triggered an NF-κB-mediated pro-inflammatory signature in articular chondrocytes, suggesting a pro-inflammatory role for this lectin in the pathogenesis of osteoarthritis (Toegel et al. 2016). In this regard, a cross-regulation has been described between Gal-1 and NF-κB transcription factor, demonstrating their interdependence in inflammatory and hypoxic microenvironments (Toscano et al. 2011, Croci et al. 2012). Further studies should be aimed at investigating the molecular bases underlying the anti-inflammatory effects of Gal-1 in immune cells versus its pro-inflammatory activity in osteoarticular chondrocytes.

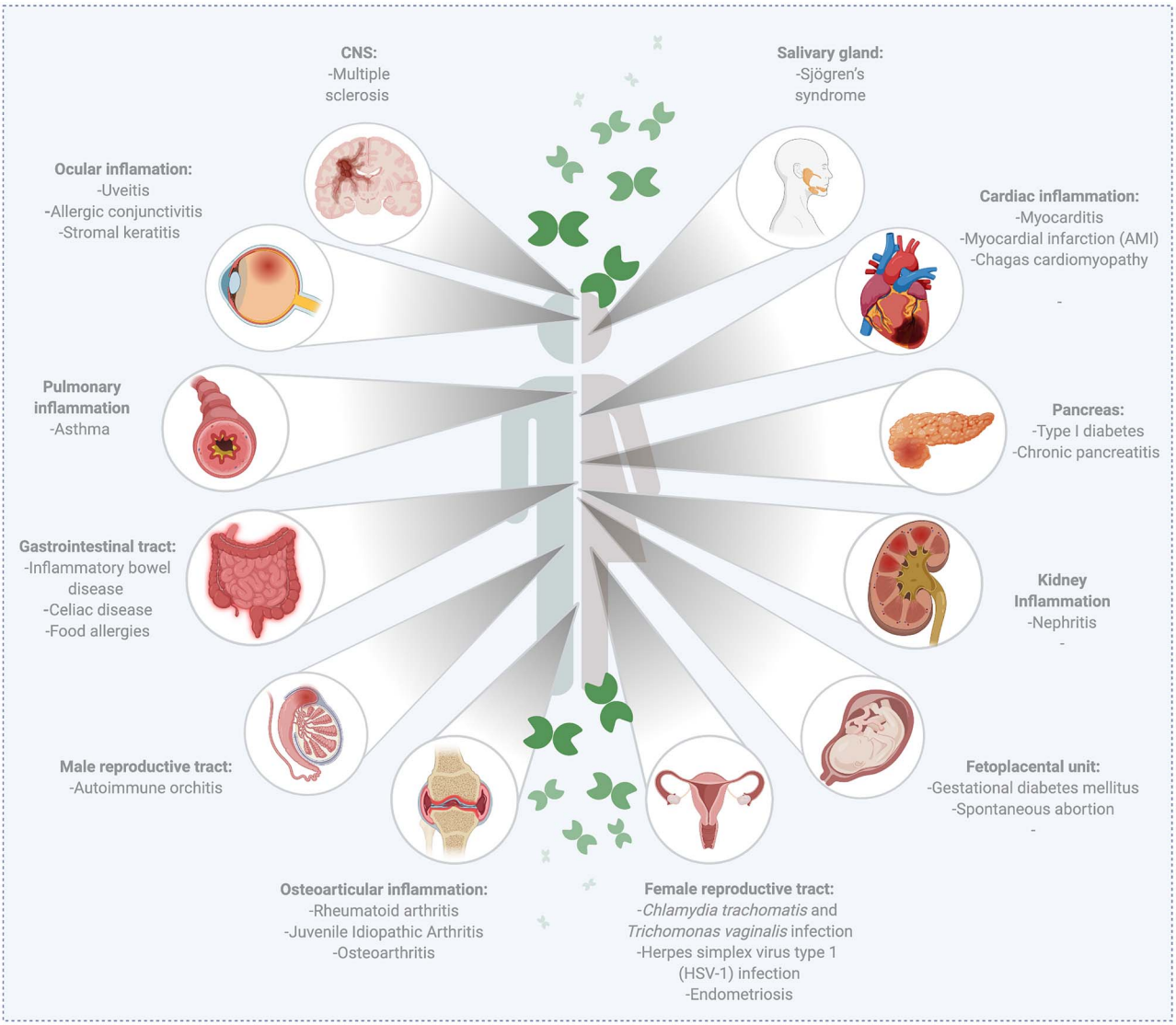

Fig. 3. Tissue-dependent regulation of inflammatory responses by Gal-1. Differential regulation of inflammatory responses by Gal-1 in different tissues and pathologic settings as detailed in the text. Created with BioRender.com. This figure is available in black and white in print and in colour at *Glycobiology* online.

Cardiac inflammation

Myocarditis is an inflammatory process of the heart muscle, which can be acute or chronic in nature and can be caused by pathogens, autoimmune stimuli and toxins. Emerging roles for Gal-1 have been identified in cardiovascular diseases, including acute myocardial infarction (AMI), heart failure, Chagas cardiomyopathy, pulmonary hypertension and ischemic stroke (Seropian et al. 2018).

Expression of Gal-1 was upregulated during AMI, an inflammatory condition, characterized by a storm of cytokines and a dysregulation of immune-mediated mechanisms, (Seropian et al. 2013). Gal-1-deficient mice showed adverse ventricular remodeling after AMI, with increased cardiac dilation associated with dysregulated uncontrolled inflammation. Lack of Gal-1 led to increased cardiac infiltration by T lymphocytes, macrophages and NK cells, while immunosuppressive Tregs were significantly reduced (Seropian et al. 2013). Additionally, Gal-1 was upregulated in postmortem hearts from Chagas cardiomyopathy patients (Giordanengo et al. 2001). Furthermore, this lectin controlled invasion and inflammation following *Trypanosoma cruzi* infection (Benatar et al. 2015), suggesting a critical role for this lectin in heart-associated inflammatory disorders.

Conclusions and future perspectives

In this review, we discussed the role of Gal-1 and its glycosylated ligands in the regulation of inflammation in different tissues, including the CNS, salivary glands, pancreas, eye, intestine, endometrium, testes, placenta, kidney, lung, synovia and heart tissue, and a broad range of pathophysiologic conditions, including cancer, neuroinflammation, sialadenitis, pancreatitis, diabetes, uveitis, IBD, endometriosis, orchitis, pregnancy failure, nephritis, asthma, arthritis and AMI (Figures 2 and 3). Through extracellular or intracellular mechanisms, Gal-1 can reprogram innate and adaptive immune responses and recalibrate homeostatic programs, leading to the control of inflammatory reactions (Figure 1). Whereas endogenous Gal-1 exerts predominant anti-inflammatory activity by selectively

deleting pathogenic Th1 and Th17 cells, promoting tolerogenic DCs, reducing leukocyte recruitment to sites of inflammation, inhibiting migration of eosinophils and polarizing macrophages and microglia toward an M2 phenotype (Toscano et al. 2018), emerging studies demonstrated pro-inflammatory roles of this lectin in testicular pathology, osteoarthritis and sepsis (Pérez et al. 2015; Toegel et al. 2016; Russo et al. 2021), suggesting context-dependent regulation of Gal-1 function. Whether the paradoxical anti- or pro-inflammatory effects of this lectin may rely on intrinsic or extrinsic factors that could influence the stability of this protein or recognition of specific glycosylated ligands regulated in a spatio-temporal manner, remains to be elucidated. Moreover, the resultant immunoregulatory activity of this lectin may be dependent on the early or late stages of the inflammatory disease or the prevailing intracellular or extracellular functions of this lectin.

Nevertheless, due to its predominant immune inhibitory capacity, blockade of Gal-1 in inflamed TME may lead to augmented immune responses in cancer. In fact, Gal-1 contributes to create immunosuppressive and pro-angiogenic microenvironments that favor tumor progression, thus validating the use of Gal-1-specific inhibitors to unleash T cell-mediated antitumor responses and overcome aberrant angiogenesis. On the other hand, administration of rGal-1 emerges as a potential therapeutic strategy in most autoimmune diseases due to its predominant immunosuppressive effects. Additionally, in other disease states, such as hematological cancers, RA and IBD, the potential role of this lectin as a biomarker of disease prognosis needs to be further validated in clinical trials.

In conclusion, Gal-1 emerges as a soluble glycocheckpoint highly regulated in the transition from physiologic to pathologic conditions, which differentially controls inflammatory responses in a tissue- and context-dependent fashion.

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Conflict of interest statement

None declared.

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Abbreviations

AC, allergic conjunctivitis; AMI, acute myocardial infarction; AP-1, activating protein-1; BCR, B cell receptor; Bregs, regulatory B cells; CAFs, cancer-associated fibroblasts; CIA, collagen-induced arthritis; CLI, chronic liver inflammation; CNS, central nervous system; CP, chronic pancreatitis; CRD, carbohydrate-recognition domain; CTLA-4, cytotoxic T-lymphocyte antigen 4; DCs, dendritic cells; EAE, experimental autoimmune encephalomyelitis; EAU, experimental autoimmune uveitis; EC, endothelial cell; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ER, endoplasmic reticulum; GalNAc, *N*-acetylgalactosamine; ERK, extracellular regulated kinase; Gal-1, galectin-1; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HNSCC, head and neck squamous cell carcinoma; HSV, herpes simplex virus; IBD, inflammatory bowel diseases; IECs, intestinal epithelial cells; IgE, immunoglobulin E; IgG, immunoglobulin G; LacNac, *N*-acetyllactosamine; LPG, lipophosphoglycan; LPS, lipopolysaccharides; MCP-1, monocyte chemotactic protein-1; MDSCs, myeloid-derived suppressor cells; Mgat5, β1,6*N*-acetylglucosaminyltransferase 5; MHC, major histocompatibility complex; MMPs, matrix metalloproteinases; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NF-κB, nuclear factor kappa B; NK, natural killer; NO, nitric oxide; NOD, nonobese diabetic; OSCC, oral squamous cell carcinoma; PD-1, programmed cell death protein-1; PSCs, pancreatic stellate cells; RA, rheumatoid arthritis; rGal-1, recombinant galectin-1; T1D, Type I Diabetes; TAMs, tumor-associated macrophages; TCR, T cell receptor; TGF, transforming growth factor; Th, T helper; TME, tumor microenvironment; TNBS, 2,4,6-trinitrobenzene sulfonic acid; TNF, tumor necrosis factor; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor.

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