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Expanding the Universe of Cytokines and Pattern Recognition Receptors: Galectins and Glycans in Innate Immunity

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Abstract Effective immunity relies on the recognition of pathogens and tumors by innate immune cells through diverse pattern recognition receptors (PRRs) that lead to initiation of signaling processes and secretion of pro- and anti-inflammatory cytokines. Galectins, a family of endogenous lectins widely expressed in infected and neoplastic tissues have emerged as part of the portfolio of soluble mediators and pattern recognition receptors responsible for eliciting and controlling innate immunity. These highly conserved glycan-binding proteins can control immune cell processes through binding to specific glycan structures on pathogens and tumors or by acting intracellularly via modulation of selective signaling pathways. Recent findings demonstrate that various galectin family members influence the fate and physiology of different innate immune cells including polymorphonuclear neutrophils, mast cells, macrophages, and dendritic cells. Moreover, several pathogens may actually utilize galectins as a mechanism of host invasion. In this review, we aim to highlight and integrate recent discoveries that have led to our current understanding of the role of galectins in host–pathogen interactions and innate immunity. Challenges for the future will embrace the rational manipulation of galectin–glycan interactions to instruct and shape innate immunity during microbial infections, inflammation, and cancer.

Keywords Microbes · innate immunity · galectins · neutrophils · macrophages · mast cells · dendritic cells · glycoimmunology · pattern recognition receptors · cytokines

Introduction

Studies performed over the past decade have been immensely fruitful in terms of advancing our understanding of the cellular and molecular mechanisms involved in innate immune responses. These include the identification of a large repertoire of pattern recognition receptors (PRRs), which can selectively discriminate among pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) that help to orchestrate and tailor immune responses [1]. These diverse receptors comprise a broad range of signaling PRRs, such as Toll-like receptors (TLRs) and NOD-like receptors, which relay extracellular information into immune signaling processes, and endocytic PRRs which promote the attachment, engulfment, and destruction of microorganisms by phagocytes [1]. Among the latter, a biochemically heterogeneous family of C-type lectin receptors (CLRs), which include among others the mannose receptor, dectin-1, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, and

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macrophage galactose lectin, have been shown to recognize specific glycans on the surface of pathogens and tumors [2, 3]. Following recognition of specific glycoepitopes, CLRs can trigger distinct signaling pathways that favor the expression of an array of cytokines and the activation of specific transcription factors [3, 4]. In contrast, a number of PRRs including complement receptors, collectins (e.g., mannan-binding lectin) and pentraxins (serum amyloid and C-reactive protein) do not remain associated with cells but are instead secreted to the extracellular milieu to recognize specific PAMPs or DAMPs [5].

Under this complex scenario, galectins have emerged as soluble lectins also capable of decoding glycan information contained in microbes and tumors [6]. Galectins are evolutionarily conserved glycan-binding proteins with multiple roles in innate and adaptive immune responses. To date, 15 galectins have been identified in mammals, most with wide tissue distribution, although some galectins are expressed with restricted tissue specificity [7]. Within the immune system, galectins are expressed by almost all immune cells, either constitutively or in an inducible fashion and are significantly upregulated in inflammatory macrophages, dendritic cells (DCs), mast cells, decidual natural killer (NK) cells, and $CD4^+CD25^+$ T regulatory (T_{Reg}) cells [8–12]. Galectins share a common structural fold and at least one conserved carbohydrate-recognition domain (CRD) of about 130 amino acids that mediates carbohydrate binding. A traditional classification based on structural similarities includes: (a) "proto-type" galectins (galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15) which have one CRD and occur as monomers or dimers; (b) "tandem repeat-type" galectins (galectin-4, -6, -8, -9, and -12) which are comprised of two different CRDs separated by a linker of up to 70 amino acids; and (c) the "chimera-type" galectin-3 which contains a CRD connected to a non-lectin N-terminal region [13]. A common structural motif recognized weakly by most galectins is the disaccharide *N*-acetyl-lactosamine (Galβ1,4GlcNAc; LacNAc), which is found in many *N*- and *O*-linked glycans and may be presented as multiple units (poly-LacNAc) on cell surface glycoproteins [14]. However, important differences in glycan-binding specificities beyond this disaccharide have been described among different members of the family that underscore the basis for functional divergences in biological activity [14]. These variations in glycan recognition are mainly associated with the extent of *N*-glycan branching, the multiplicity of LacNAc residues, the modification of terminal saccharides, and/or the protein or lipid scaffold of glycoconjugates [14]. Most galectins are either bivalent or multivalent with regard to their glycan-binding activities, which enable recognition of multiple binding partners and activation of distinct signaling pathways; one-CRD galectins can dimerize, two-CRD galectins are at least bivalent, and galectin-3 can form oligomers upon binding to multivalent glycoproteins [13]. Although galectins do not contain a classical secretory signal, some members are found in the extracellular compartment and are released through an unusual route that requires intact carbohydrate-binding activity of the secreted protein [13]. Once externalized, galectins can bind to multiple glycosylated-binding partners on microbial pathogens or host cells and convey glycan-containing information into innate immune cell programs [15, 16]. However, this activity is limited to those galectins that are secreted into the extracellular milieu; some members of the family may remain associated with cell membranes or function primarily within the intracellular compartment [17], suggesting both intracellular and extracellular roles for these endogenous lectins. As other review articles have extensively covered the contribution of galectins to adaptive immunity in greater depth [6, 18, 19], we will underscore here recent insights into the mechanisms by which galectins and their specific saccharide ligands contribute to pathogen recognition and innate immune responses.

Galectins in Host–Pathogen Interactions and Innate Immunity

Complex carbohydrates dominate the surface of pathogens, and thus it is not surprising that many innate immune factors evolved glycan-binding properties as a mechanism of pathogen recognition. Indeed, many factors associated with activation of immunity display glycan-binding activity. Recent studies suggest that galectin family members, as well as CLRs, may also serve as pathogen recognition receptors (PRRs) [20]. For example, Gal-3 can bind to glycans expressed by *Neisseria gonorrhoeae*, *Leishmania major*, *Schistosoma mansoni*, and *Trypanosoma cruzi* [21–24]. Given the ability of Gal-3 to uniquely associate with macrophages [25], engagement of different pathogens by Gal-3 may not only facilitate immune activation but may also mediate phagocyte recognition and removal. In this regard, recent findings demonstrated that binding of *Toxoplasma gondii* glycosylphosphatidylinositols to Gal-3 in macrophages is required for parasite recognition and TNF production [26].

While engagement of pathogens by galectins may serve in part to activate immunity, several studies suggest that galectins may provide direct innate immune function. For example, Gal-3 can recognize distinct pathogenic mycotic species, such as *Candida albicans*, while failing to recognize nonpathogenic *Saccharomyces cerevisiae* [27, 28]. Importantly, Gal-3 recognition results in significant

loss of *C. albicans* viability [28]. Recognition appears to occur through specific interactions with α1-2-type mannans [27, 28], a unique sugar sequence motif of fungi previously unrecognized as a ligand for galectins. By contrast, while Gal-1 may not directly alter viral viability, Gal-1 appears to provide some degree of protection from the pathogenic sequelae associated with Nipah virus infection. Recent studies suggest that Gal-1 specifically inhibits Nipah virus-mediated cellular syncytia formation [29, 30], a process that can result in significant morbidity and mortality secondary to systemic vasculitis [31].

Although innate immune factors commonly discriminate self from non-self by recognizing PAMPS, several pathogens appear to uniquely generate self-like antigens [1, 4], which might be thought of as a type of molecular mimicry. As central tolerance mechanisms result in the deletion of potentially self-reactive cells [32], the defense mechanism whereby an individual is protected against pathogens decorated with self-like antigens remained unknown. Although galectins can recognize glycan antigens unique to pathogens [27, 28], some galectins also display significant affinity for self-antigens. Consistent with this, recent studies demonstrated that several galectins, in particular, Gal-4 and Gal-8, display high affinity for human ABO (H) blood group antigens [33, 34]. Given the reduced ability of a blood group positive individual to provide humoral immunity against cognate blood group antigens on pathogens, these results suggested that Gal-4 and Gal-8 might be uniquely poised to provide immunity against blood group bearing pathogens, irrespective of the blood group status of an individual. Unexpectedly, recent results demonstrated that Gal-4 and Gal-8 recognize and kill blood group positive *Escherichia coli* [35]. This innate immune activity appears to be specific to blood group positive pathogens because it was observed that Gal-4 and Gal-8 fail to recognize or kill related bacteria that fail to express the blood group antigen or bacteria expressing mutations in the LPS biosynthetic pathway, leading to loss of blood group antigen synthesis. Engagement of blood group B-positive pathogens by Gal-4 and Gal-8 results in rapid loss in mobility, significant alterations in membrane architecture, and loss of membrane integrity [35]. While recognition of the specific blood group B antigen on the surface is necessary for Gal-4- and Gal-8-induced killing, recognition alone does not result in loss of viability; for example, Gal-3, which also recognizes blood group B-positive *E. coli,* fails to alter viability [35]. Taken together, these results provide one of the first striking examples of an innate immune factor that recognizes a distinct self-like antigenic target on the surface of a pathogen and provides a possible mechanism whereby individuals might protect themselves against a blood group positive pathogen irrespective of their own blood group status.

Unlike the innate immune effects proposed previously, several studies suggest that galectin–pathogen interactions could also mediate pathogen adhesion and therefore facilitate infection. For example, several key studies demonstrated that Gal-1 can significantly alter cellular sensitivity toward HIV infection by stabilizing HIV interactions at the plasma membrane [36, 37]. Importantly, Gal-1-mediated enhancement of viral infection may not be limited to HIV. A recent study suggested that Gal-1 may play a similar role in HTLV infection [38]. Similarly, Gal-1 appears to facilitate *Trichomonas vaginalis* infection by providing an adhesion contact to cervical epithelium [39]. Moreover, Gal-3 may also enhance infection by enabling *Helicobacter pylori* adhesion to gastric epithelium [40].

While the majority of studies examined the activity of galectins against human pathogens, interactions between galectins and pathogens appear to be highly conserved. For example, while Gal-3 may serve as a PRR in the detection of *L. major* infection in humans [23], a similar tandem-repeat galectin, PpGalec, found in the midgut of the sandfly *Phlebotomus papatasi*, appears to mediate attachment and survival of *L. major* in this key vector [41]. Similarly, Gal-9 may also promote infection by facilitating *L. major* adhesion in humans [42]. In contrast, a galectin from the mushroom *Coprinopsis cinerea* appears to provide innate immunity against *Caenorhabditis elegans* through recognition of a unique terminal galactose-containing core *N*-glycan structure [43]. Taken together, these results demonstrate that various galectin family members likely play a wide variety of roles within innate immunity and that several pathogens may actually utilize galectins as a mechanism of host invasion (Figs. 1 and 2).

Galectin Regulation of Neutrophil Turnover

Cellular turnover represents a fundamental immunological homeostatic process. Following a pathogenic challenge, significant recruitment of leukocytes involved in both innate and adaptive immunity enables neutralization of invading pathogens. However, in order for effective homeostasis to be maintained, significant leukocyte contraction must occur in order to prevent damage of viable tissue and reduce the probability of autoimmunity [44]. Several key players may be important in regulating leukocyte viability and turnover. For example, TNF family members appear to induce apoptosis in distinct lymphocyte populations [45]. Indeed, individuals with mutations in the TNF family member Fas develop autoimmune lymphoproliferative syndrome (ALPS), a disorder characterized in part by significant accumulation of lymphocytes [46, 47].

Although lymphocytes appear to be dependent on factors that induce apoptotic cell death, neutrophils may have evolved

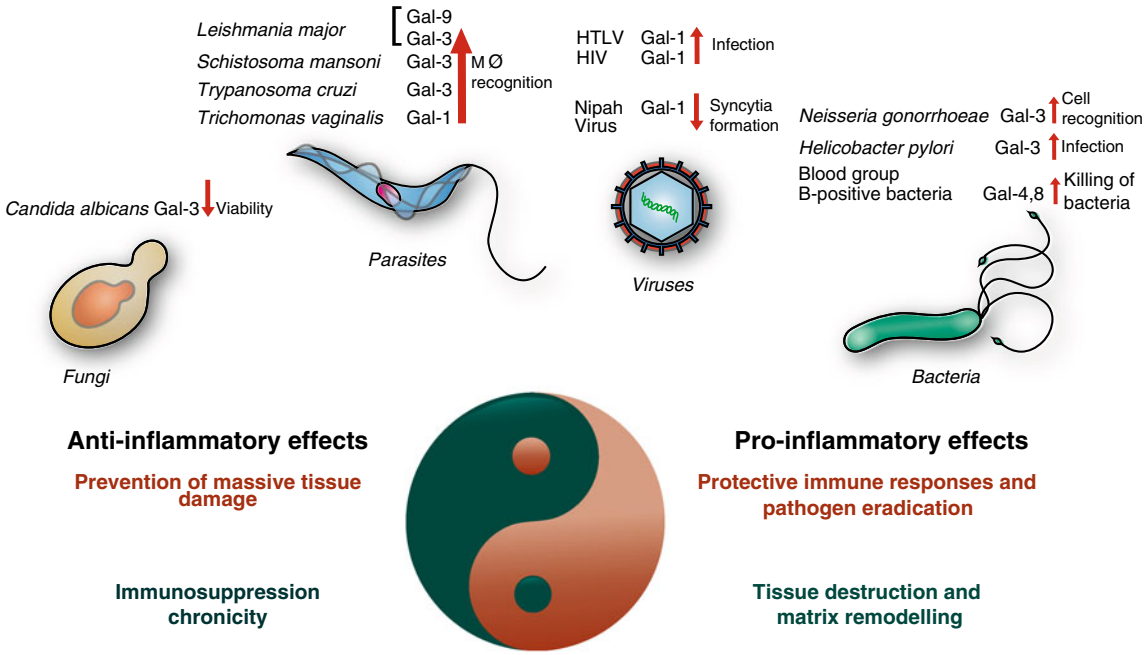

Fig. 1 The "yin-yang" of galectins in host–pathogen interactions and innate immunity. Through specific recognition of glyco-epitopes that are either restricted to pathogens or shared by host cells, galectins can favor pro-inflammatory responses and pathogen eradication or foster immunosuppressive microenvironments that may facilitate chronic infection. A thorough understanding of galectin–glycan interactions at the host–pathogen interface may help to capitalize this information for immunotherapeutic or vaccination protocols

a unique apoptosis-independent mechanism of turnover. Individuals with ALPS often display reduced neutrophil numbers, and mice deficient in Fas or FasL display normal numbers of neutrophils prior to and during inflammatory events [46–49]. Neutrophils in mice engineered to over express Bcl-2 in myeloid cell lines exhibit significant resistance to apoptotic cell death, yet fail to display altered baseline numbers and remain sensitive to phagocytosis in vivo [50]. Consistent with this, non-apoptotic neutrophils appear to be phagocytosed during normal neutrophil turnover [51].

Although previous studies clearly demonstrated that neutrophils undergo turnover independent of apoptosis in vivo, the mechanism responsible for this turnover remained unknown. Recent studies suggest that several galectin family members may specifically induce apoptosis-independent removal of neutrophils. During the early stages of apoptosis, cells commonly externalize phosphatidylserine (PS), a phospholipid normally confined to the inner leaflet of the plasma membrane [52], which has therefore been considered a death signal. However, independently of being an apoptotic marker, cell surface PS serves as a key ligand for macrophage-mediated phagocytosis [53]. Similar to cells undergoing apoptosis, it was recently shown that several galectin family members, including Gal-1, Gal-2, Gal-3, Gal-4, and Gal-8 induce PS exposure in activated, but not resting, neutrophils [54–57]. However, unlike cells undergoing apoptosis, galectin-induced PS exposure occurs independently of cell death. For example, despite inducing PS exposure, Gal-1 fails to induce DNA fragmentation, mitochondrial potential changes, or alterations in membrane architecture or integrity [55, 56]. Furthermore, PS exposure induced by Gal-1 also reverses following Gal-1 removal [54, 56]. Consistent with this, Gal-1-induced PS exposure occurs independent of common irreversible processes associated with apoptosis, such as caspase activation or an accompanying loss of membrane integrity [56]. Although galectins appear to induce PS exposure in neutrophils independent of cell death, galectin-induced PS exposure sensitizes cells to phagocytic removal by macrophages [55, 56], which represents one of the first examples of targeted phagocytic removal of a living cell. In addition, Gal-3 may directly facilitate clearance of neutrophils by directly enhancing macrophage-mediated phagocytosis [58]. Because galectins fail to induce cell death, yet sensitize cells to phagocytic removal, this unique activity was recently coined "preaparesis" [59], signifying the ability of galectins to prepare cells for removal without directly inducing apoptotic cell death.

In addition to the proper regulation of neutrophil turnover, immunological homeostasis requires significant regulation of neutrophil activation and recruitment. Endothelial cells play a central role in the proper activation, localization, and extravasation of neutrophils to an area of tissue injury or pathogen invasion [60]. Although previous studies predominately focused on the roles of selectins and integrins in the regulation of neutrophil extravasation [60, 61], several recent studies implicate various galectin

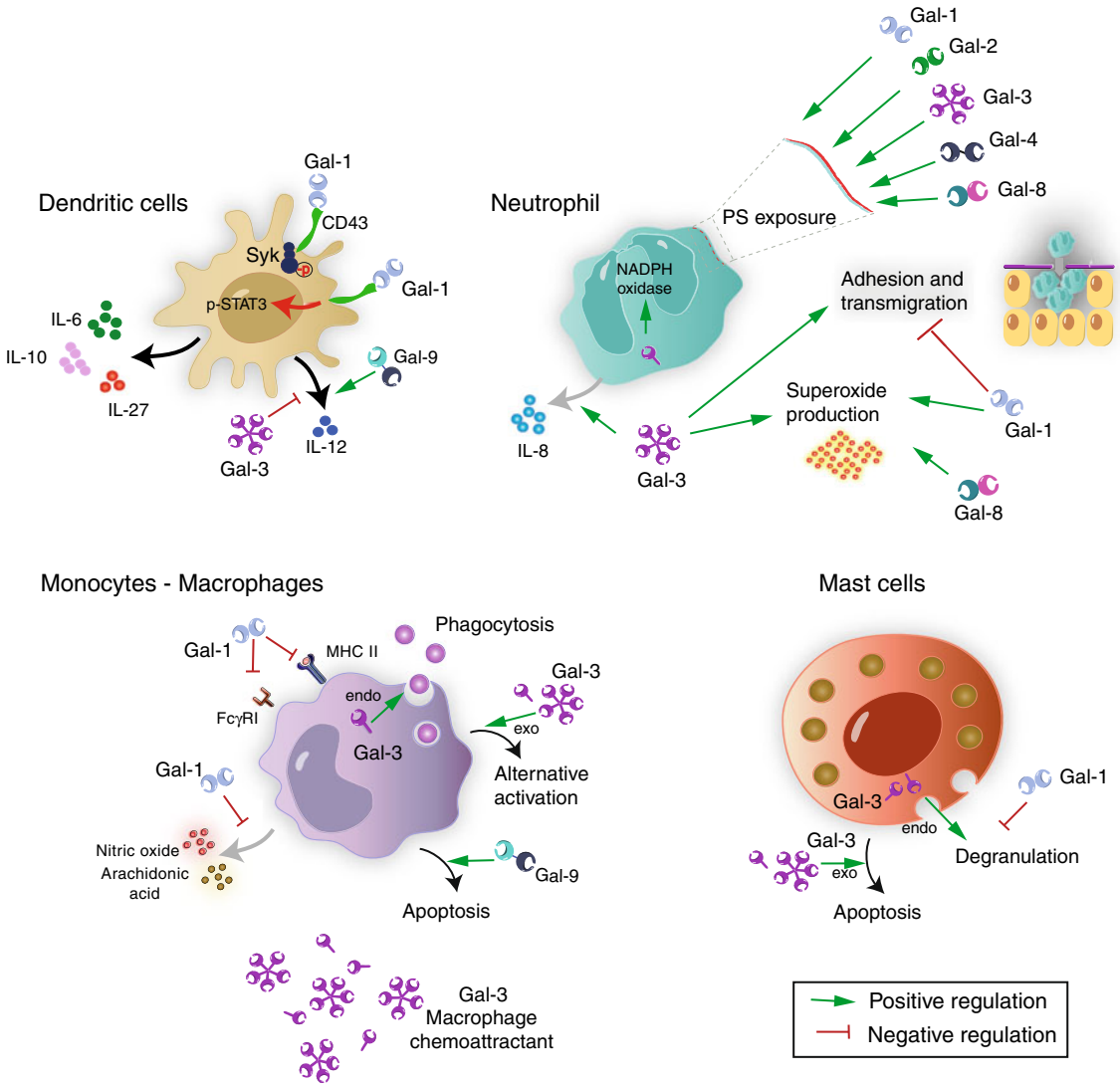

Fig. 2 Galectins in innate immunity. Galectins influence a variety of biological processes of cells participating in innate immunity either in an extracellular or intracellular fashion. The functions illustrated here have been demonstrated by in vitro exposure to recombinant galectins, targeted delivery of galectins in vivo, or following challenge of galectin-deficient mice. While Gal-1 inhibits neutrophil transmigration through extracellular matrix, Gal-3 favors neutrophil adhesion to endothelia through its oligomerization processes. Galectins also affect the function of neutrophils by promoting phosphatidylserine (PS) exposure without inducing apoptosis, and regulating superoxide and IL-8 production. In addition, galectins can affect the functional fate of monocytes/macrophages by skewing the balance toward alternative versus classical activation, controlling nitric oxide production, and regulating FcγRI-mediated phagocytosis and MHC II-dependent antigen presentation. Furthermore, Gal-3 contributes to monocyte/macrophage chemotaxis and phagocytosis. Emerging evidence also indicates a role for galectins in the control of mast cell function. Endogenous and exogenous Gal-3 promotes mast cell activation and degranulation. However, indirect evidence gathered in vivo indicates that Gal-1 blocks mast cell degranulation, but mechanisms are unknown. Interestingly, while Gal-1 promotes DC maturation and migration, it also instructs these cells to become tolerogenic and secrete high amounts of IL-27 and IL-10. Of note, Gal-3 inhibits whereas Gal-9 stimulates IL-12 production by DCs. Thus, galectins modulate innate immune reactions through a plethora of mechanisms, including the control of adhesion and transmigration through endothelial cell surfaces, the ability to recognize, engulf, and kill intruders and damaged cells and the capacity to produce pro- and anti-inflammatory cytokines and respond to chemotactic gradients

family members in this process. Such studies suggest that Gal-1 can significantly inhibit extravasation of neutrophils in vitro and in vivo [62, 63]. Unlike selectins, Gal-1 may regulate neutrophil extravasation at the level of transmigration [63]. Recombinant delivery of Gal-1 prevents neutrophil extravasation in vivo, and Gal-1 null mice experience enhanced neutrophil emigration [62, 63]. Furthermore, once neutrophils extravasate, Gal-1 appears to inhibit their chemotaxis [63]. By contrast, Gal-3 appears to mediate neutrophil attachment to vascular endothelial cells following *Streptococcus pneumoniae* infection [64]. Gal-3 null mice experience a significant reduction in

neutrophil accumulation within the lung following infection with *S. pneumoniae* [65]. Importantly, these later studies provide a few of the only genetic studies demonstrating a role of galectins in neutrophil regulation in vivo [62, 65].

In addition to regulating neutrophil viability and recruitment, earlier studies examining the impact of galectins on neutrophils demonstrated that several galectin family members also regulate neutrophil activation [66]. Gal-3 activates NADPH-oxidase, a key factor in the microbicidal activity of neutrophils [67], in exudated but not peripheral neutrophils [66, 68]. Exudation and LPS engagement of neutrophils appears to increase the expression of cell surface Gal-3 ligands and sensitizes cells to Gal-3-mediated activation of the respiratory burst [66, 69] and neutrophil-mediated phagocytosis [68]. In turn, Gal-3 appears to sensitize neutrophils to soluble fibrinogen [68]. Subsequent studies identified CD66a and CD66b as potential ligands for Gal-3-mediated neutrophil activation [70]. Galectin-mediated activation of neutrophils does not appear to be limited to Gal-3 as recent studies suggest that Gal-1 may induce similar alterations in neutrophil activity [71].

The unique nature of the inflammatory environment that surrounds neutrophil-mediated immunity likely selected for distinct roles for galectin family members in neutrophil activation, recruitment, and turnover. Endothelial expression of galectins likely enables regulation of neutrophil activation and extravasation [72–74]. However, once neutrophils accumulate at specific sites following tissue injury, inflammatory resolution is dependent on effective removal. However, neutrophil numbers often far outweigh the number of macrophages responsible for removing them [75]. Indeed, ineffective removal and excessive neutrophil necrosis often significantly impairs inflammatory resolution and can contribute to abscess formation [76]. The unique localization of galectin family members within tissue parenchyma likely enables them to inhibit neutrophil chemotaxis and facilitates neutrophil turnover, potentially allowing for important demarcation of viable from necrotic tissue [63, 74]. The unique ability of galectins to induce an "eat me" signal without causing cell death by the process of "preaparesis" may also allow neutrophils to maintain membrane integrity in a relatively harsh inflammatory environment until successfully phagocytosed [76]. These results demonstrate that galectin family members likely play key roles at a variety of checkpoints necessary for proper regulation of neutrophil function.

Galectin-Mediated Control of Mast Cell Degranulation and Function

Mast cells play essential roles at the interface of innate and acquired immunity [77]. These cells release a large number of mediators and cytokines when activated by IgE, anaphylatoxins, and/or products derived from either pathogens or the host during innate immune responses. Although best known for their role in allergic disorders, mast cells can also exacerbate models of autoimmunity, play a role in tumor immunity, and increase inflammation during bacterial infections. In other settings, however, mast cells can limit inflammation and tissue injury [77]. Gal-3 was earlier identified as an IgE-binding protein capable of binding mast cells and basophils [78], thus it was not surprising to find that this lectin plays crucial roles in mast cell physiology. Upon cross-linking of FcεRI, Gal-3-deficient mast cells secrete lower amounts of histamine and IL-4 than wild-type mast cells [10]. Accordingly, Gal-3 null mice showed reduced passive cutaneous anaphylaxis reactions in vivo compared to wild-type littermates [10]. While intracellular Gal-3 stimulates mast cell function, extracellular Gal-3 induces mast cell apoptosis [79], suggesting a dual role for the intracellular or extracellular lectin in regulating cell fate. Moreover, injection of Gal-1 in a model of rat hind paw edema reduces mast cell degranulation through still unresolved mechanisms [80] consistent with the well-established anti-inflammatory function of this lectin [19]. Recent studies involving RBL-2H3 cells demonstrated that Gal-9 suppresses mast cell degranulation through mechanisms involving inhibition of IgE–antigen complex formation. These results were further verified in vivo showing attenuation of asthmatic and cutaneous anaphylactic reactions following Gal-9 administration [81]. Thus, galectins control mast cell physiology through different mechanisms involving positive or negative regulation of granule release, IgE–antigen complex formation and survival. Given the broad expression of Gal-1, Gal-3, and Gal-9 in peripheral tissues [13], it is likely that the synchronized action of these lectins together with chemokines, cytokines, and IgE determines the fate and function of mast cells.

Galectins Shape Macrophage Function and Plasticity

Monocytes and macrophages are key cellular components involved in resistance to pathogens, tissue repair, and cancer surveillance [82]. Macrophages display remarkable plasticity and can change their physiology in response to environmental cues, giving rise to three versatile populations with distinct biological functions. "Classically activated" macrophages arise in response to IFN-γ and produce high levels of IL-12 and modest levels of IL-10. By contrast, "regulatory macrophages" are generated in response to immune complexes, prostaglandins, or glucocorticoids and produce high levels of IL-10 and low levels of IL-12. On the other hand, macrophages treated with IL-4 ("alternatively activated" or "wound-healing" macro-

phages) produce low levels of IL-12 and IL-10 but express resistin-like molecule-α (RELM-α) intracellularly, a marker that is not expressed by the other macrophage populations. Whereas "classically activated" macrophages display microbicidal activity and favor tissue damage, "regulatory macrophages" suppress immune reactions and "alternatively activated" macrophages play a key role in tissue repair, angiogenesis, and Th2-type cytokine skewing [83]. The broad expression of galectins within the monocyte/macrophage compartment [8, 84, 85] together with their localization in inflammatory and tumor microenvironments suggested that these proteins might play a role in modulating macrophage physiology.

Early studies demonstrated that exposure to Gal-1 shifts the balance toward "alternatively activated" or "regulatory" macrophages as demonstrated by increased arginase activity [86] and PGE2 production [80]. Subsequent studies have shown that Gal-1 acts on monocytes/macrophages by regulating critical regulatory molecules such as Fcγ receptor 1 (FcγR1) and major histocompatibility complex (MHC)-II and modulates essential functions including phagocytosis and antigen presentation [87]. In addition, exposure to Gal-1 inhibits IL-12 production and enhances IL-10 production by parasite-infected macrophages [88]. Importantly, Gal-1 does not affect survival of human monocytes even following activation but instead can modulate macrophage activity through ERK1/2-dependent pathways. These effects were also apparent in macrophages recruited in response to inflammatory stimuli following treatment with Gal-1 and were further confirmed in Gal-1-deficient (*Lgals1*$^{-/-}$) mice [87]. More recently, studies highlighted an unexpected role for Gal-1 in facilitating viral adsorption to macrophages during HIV-1 infection [37], suggesting that blockade of this protein might play a role in viral–host cell interactions.

On the other hand, Gal-3 displays multifaceted roles within the macrophage compartment [89]. In fact, Gal-3 serves as a selective chemoattractant for macrophages [90], functions as an opsonin [58, 91], and triggers the production of reactive oxygen species by macrophages and monocytes [92, 93]. In addition, Gal-3 activates microglial cells and macrophages to phagocytose degenerated myelin in the central nervous system [94]. Interestingly, recent studies examining the mechanisms underlying these immunoregulatory effects demonstrated that this lectin exerts cytokine-like regulatory actions in brain-resident microglia/macrophages through induction of pro-inflammatory mediators and regulated expression of signaling pathways including JAK2 and STAT1, STAT3, and STAT5 [95]. Interestingly, Gal-3 significantly induces phosphorylation of STATs in microglia from IFN-γ-deficient mice, suggesting that this effect is independent of IFN-γ, a canonical activator of the JAK-STAT pathway [95]. These findings provide a rational explanation for the pro-inflammatory effects induced by Gal-3. Interestingly, macrophages from Gal-3-deficient (*Lgals3*$^{-/-}$) mice showed reduced IL-4-induced alternative macrophage activation in vitro compared to those from wild-type macrophages, but the two genotypes were comparable in IFN-γ/LPS-induced classical activation and IL-10-induced deactivation [96]. Recombinant Gal-3 also promoted IL-4-induced alternative activation [96], suggesting that it might be a general function of galectins to selectively control the state of macrophage activation. On the other hand, Gal-9 induces apoptosis of a monocytic cell line (THP-1) and transactivates pro-inflammatory cytokine genes in monocytes by functioning intracellularly [97]. Moreover, a recent study demonstrated that Gal-9, which is expressed by *Mycobacterium tuberculosis*-infected macrophages, interacts with Tim3 expressed on Th1 cells to restrict intracellular bacterial replication [98]. The Gal-9–Tim-3 interaction leads to macrophage activation and stimulates bactericidal activity by stimulating caspase-1-dependent IL-1β secretion [98]. Thus, galectins can endow macrophages with antimicrobial, pro-inflammatory, or immunoregulatory functions at the cross-road of innate and adaptive immune responses.

Circuits of Galectins and Glycans in the Regulation of DC responses

DCs are the central players in all immune responses, both innate and adaptive [99]. Conventional DC subsets described in humans include myeloid DCs and plasmacytoid DCs [99]. Pioneering studies demonstrated that DCs are important in orchestrating adaptive immune responses through their ability to capture, process, and present antigens to naïve T cells [99]. However, in recent years, there has been a shift from the perception of DCs solely as inducers of immune reactivity to the view that these cells are crucial regulators of immunity, which includes their ability to induce and maintain tolerance [100, 101].

During microbial infection or tumor establishment, different mechanisms take place to initiate either an immunogenic or tolerogenic pathway [102]. In explorations of possible mechanisms underlying the broad anti-inflammatory activities of Gal-1 [18], recent studies demonstrated that DCs differentiated or matured in a Gal-1-enriched microenvironment acquire a distinctive "regulatory signature" characterized by high expression of the cell surface marker CD45RB, phosphorylation of the transcription factor STAT3, and abundant secretion of IL-27 and IL-10 [9]. More importantly, when transferred in vivo, these DCs promoted T cell tolerance in antigen-specific and neoplastic settings, blunted Th1 and Th17

responses, and halted autoimmune inflammation through mechanisms involving DC-derived IL-27 and T cell-derived IL-10 [9]. This immunoregulatory circuit linking Gal-1 signaling, IL-27-producing tolerogenic DCs and IL-10-secreting T_{reg} cells may operate during microbial infection, resolution of autoimmune disorders, and tumor settings [9]. Remarkably, Gal-1 expression is augmented during the peak of inflammation and is dramatically up-regulated by tolerogenic stimuli including vasoactive intestinal peptide, vitamin D3 and IL-10 but significantly downregulated by pro-inflammatory cytokines (TNF and IFN-γ) and most TLR agonists [9]. Such results suggest that the Gal-1-glycan axis might operate during the resolution of immune responses. Moreover, DCs lacking Gal-1 had lower expression of IL-27, higher expression of IL-23 and less STAT3 phosphorylation, and were much more immunogenic than their wild-type counterpart [9]. In accordance with these findings, injection of recombinant Gal-1 favored the recruitment of a subset of uterine DCs with a tolerogenic phenotype [103]. Moreover, other studies demonstrated that exposure to Gal-1 promoted the maturation and migration of DCs through mechanisms involving Syk and PKC signaling [104]. Gal-1 stimulated Syk phosphorylation and recruitment of phosphorylated Syk to CD43 and CD45 glyco-receptors on monocyte-derived DCs to regulate DC activation and migration across extracellular matrix. Remarkably, intradermal injection of Gal-1 in *MRL-fas* mice, which have a defect in skin DC emigration, increased the in vivo migration of dermal DCs to draining lymph nodes [104], suggesting that DCs exposed to Gal-1 may acquire a distinctive immunoregulatory program characterized by a "mature" or "immature" cell surface phenotype, increased migration profile, and enhanced tolerogenic potential. Thus, in the presence of Gal-1, DCs may undergo maturation and migrate to peripheral tissues to promote immune tolerance, further emphasizing the lack of correlation between the maturation state of DCs and their immunogenic or tolerogenic potential [19]. Similarly, DCs lacking Gal-3 secrete higher amounts of IL-12 than wild-type DCs and favor the polarization of T cells toward a Th1-type profile [105, 106], suggesting a common mechanism by which endogenous galectins may control DC immunogenicity. In addition, endogenous Gal-3 can also regulate the trafficking pattern of DCs through intracellular mechanisms involving control of membrane ruffles [107]. Furthermore, DCs exposed to Gal-9 produce higher levels of IL-12 and are endowed with Th1-type polarizing potential [108]. Interestingly, DC maturation is accompanied by pronounced changes in glycan expression which might affect binding of galectins to the surface of these cells [109]. Collectively, these data imply divergent roles of galectins in the control of DC maturation, trafficking pattern, and immunogenicity.

Conclusions and Future Directions

Pattern recognition receptors sense microbial components to trigger innate immune responses, the first line of host defense against infectious agents and tumor antigens. However, aberrant activation of immune cell components often causes massive inflammation, leading to the development of autoimmune diseases. Therefore, both activation and inactivation of innate immune responses must be strictly controlled to limit tissue damage [1–3]. Here, we described the consequences of galectin signaling as it relates to host–pathogen interactions and innate immune cell functions. While some members of the galectin family can influence initiation of immune responses through facilitating phagocytosis, chemotaxis, granule release, and pro-inflammatory cytokine secretion, under certain circumstances, galectins may also contribute to the resolution of acute inflammation by preparing neutrophils for phagocytic removal, inhibiting neutrophil transmigration and driving the differentiation of regulatory DCs and "alternatively activated" macrophages. Similar to what has been observed for many cytokines and growth factors, it is not surprising that galectins may exhibit "double-edge sword" effects with opposing biological outcomes depending on different intrinsic factors such as the physicochemical properties of the protein (monomer/dimer equilibrium), stability of the protein in oxidative versus reducing microenvironments, as well as extrinsic factors such as the target cell type and its activation or differentiation status.

Additionally, we have illustrated several examples of pathogens that bind host galectins through glycan-mediated interactions and trigger immune cell signaling processes. Particularly, we have underscored one of the first striking examples of innate immune factors (Gal-4 and Gal-8) that recognize a distinct self-like antigenic target on the surface of a pathogen and provides a possible mechanism whereby individuals might protect themselves against a blood group positive pathogen irrespective of their own blood group status. Follow-up studies are needed to examine the mechanism of bacterial killing by galectins and the larger physiological significance of this activity in regulating the microbiome and limiting growth of pathogenic microbes.

In vivo studies, including those using galectin-deficient mice, have begun to provide relevant information on the selective function of these endogenous lectins in microbial invasion, tumor progression, and autoimmunity, suggesting their potential use as adjuvants or antagonists in immunotherapeutic regimens. However, before galectin-based therapeutic agents can be embraced, a more thorough understanding of the mechanisms involved in galectin functions is essential. In this regard, it will be critical to evaluate the results of "side-by-side" studies of the biological activities of different members of the galectin

family and their regulated expression in healthy, infected, or neoplastic tissue. Attention should also be focused to understand the importance of natural anti-galectin autoantibodies in sera from patients with autoimmune disorders versus unaffected individuals [110]. Given the complexity of galectin–glycan interactions and the multiple parameters influencing these molecular contacts, further work is required, involving multidisciplinary approaches, to achieve a global comprehensive view of the role of endogenous galectins and their specific carbohydrate ligands in host–pathogen interactions and innate immunity.

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