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Endogenous lectins shape the function of dendritic cells and tailor adaptive immunity: Mechanisms and biomedical applications

Iván D. Mascanfroni [a,1], Juan P. Cerliani [a,1], Sebastián Dergan-Dylon [a], Diego O. Croci [a], Juan M. Ilarregui [a], Gabriel A. Rabinovich [a,b,*]

[a] Laboratorio de Inmunopatología, Instituto de Biología y Medicina Experimental, Consejo Nacional de Investigaciones Científicas y Técnicas, C1428, Ciudad de Buenos Aires, Argentina
[b] Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, C1428, Ciudad de Buenos Aires, Argentina

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ABSTRACT

In spite of their central role in orchestrating immunity, dendritic cells (DCs) can also limit harmful reactions and promote immune tolerance by inducing T cell anergy or favoring the differentiation of T regulatory (T_{reg}) cells. Several factors may influence the 'decision' of DCs to become immunogenic or tolerogenic including the nature of antigenic challenge, the engagement of selective pathogen recognition receptors (PRRs) and the balance of cytokines and growth factors. In addition, mounting evidence indicates a key role of endogenous lectins including C-type lectins, siglecs and galectins in shaping DC immunogenicity and tailoring adaptive immune responses, through recognition of specific 'glycan signatures' on invading pathogens or host cells. While galectins are in general secreted proteins that act in a paracrine or autocrine manner, all known siglecs and most C-type lectins are membrane-bound receptors that convey glycan-containing information into DC differentiation or maturation programs. Yet, some of the signaling pathways triggered by endogenous lectins converge in similar functional outcomes regardless of divergences in their structure, homology or glycan-binding specificity. To gain a more complete understanding on the role of protein–glycan interactions in DC biology, here we will integrate scattered information on these structurally-divergent but functionally-related lectins and their potential biomedical applications.

1. Introduction

2. "To be or not to be": shaping the immunogenic or tolerogenic function of DCs

Studies carried out over the past decade have been immensely fruitful in terms of advances in our understanding of the cellular and molecular mechanisms that control central and peripheral immune tolerance. Important developments include the identification of gene products and molecular pathways that lead to the differentiation and expansion of regulatory myeloid cells including tolerogenic DCs [1]. DCs are bone marrow-derived professional antigen-presenting cells (APCs) which link innate and adaptive immunity and act as sentinels that monitor the extracellular space in search for foreign or dangerous proteins to be endocytosed and presented via major histocompatibility class (MHC) molecules [2]. Although originally identified by their pivotal role in orchestrating adaptive immunity, compelling evidence highlight a critical role for DCs in promoting tolerance, limiting uncontrolled inflammation and maintaining immune cell homeostasis [3,4]. A traditional view considered that the regulatory or tolerogenic profile of DCs was exclusively related to certain maturation stages or specialized DC subsets characterized by low expression of co-stimulatory molecules (CD40, CD80, and CD86), low production of pro-inflammatory cytokines (interleukin (IL)-12, IL-23 and TNF) and increased secretion of IL-10. However, recent evidence challenged the paradigm of 'fully mature DCs' eliciting adaptive immunity versus 'immature DCs' acting as promoters of T-cell tolerance, indicating that phenotypic maturation itself is not necessarily a hallmark of immunogenic versus tolerogenic DCs [5]. In fact, mature DCs usually display tolerogenic or regulatory activity when exposed to certain immunosuppressive microenvironments or distinct pathological conditions [6]. Several stimuli may influence the 'decision' of DCs to become tolerogenic, including the nature of microbial or tumor antigen recognized by different PRRs [4], the interaction with stromal cells [7] and the secretion of cytokines, neuropeptides and growth factors including IL-10, granulocyte colony-stimulating factor (G-CSF), vasoactive intestinal peptide (VIP) and 1,25-dihydroxyvitamin D3 [8–11]. Furthermore, induction of indoleamine 2,3-dioxygenase (IDO) by Toll-like receptor (TLR) ligands or CTLA-4 may endow DCs with tolerogenic potential [12]. Also, DCs can promote tolerance upon capture of antigens from dying cells [13,14]. Furthermore, DCs modified by $CD4^+CD25^+FoxP3^+$ T regulatory (T_{reg}) cells may become tolerogenic and drive the differentiation of IL-10-producing type 1 (Tr1) cells, which suggest a link among distinct regulatory cell populations [15].

* Corresponding author.
E-mail addresses: gabyrabi@gmail.com, gabriel.r@ibyme.conicet.gov.ar (G.A. Rabinovich).
[1] I.D.M. and J.P.C. contributed equally to this work.

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To elucidate whether the main role of DCs was associated to immune cell activation or tolerance, Ohnmacht and colleagues used an elegant system by generating constitutively DC-depleted mice using the diphtheria toxin A (DTA)[16]. As expected, depletion of DCs resulted in lack of priming of naïve T cells and impaired protective immunity to the parasite *Nippostrongylus brasiliensis*. This observation was consistent with the professional role of DCs as APCs and initiators of immune responses. Unexpectedly, however, these mice rapidly developed spontaneous severe autoimmunity, characterized by an inflammatory infiltrate composed of macrophages, granulocytes and pathogenic $CD4^+$ T cells in multiple organs. The frequency of IFN-γ and IL-17A-producing cells was increased by 10-fold in DC-depleted mice, whereas the frequency of peripheral T_{reg} cells was normal [16]. These observations suggest that DCs are, by themselves, essential components to maintain peripheral tolerance and that a spatiotemporal regulation of the immunogenic or regulatory activities of DCs takes places *in vivo* during the development of a normal immune response. These conclusions were further supported by recent observations showing accumulation of self-reactive T cells in peripheral lymphoid organs when DCs were defective in apoptotic cell uptake [17]. Although the signaling pathways differentially activated in tolerogenic versus immunogenic DCs remain largely unexplored, recent work from Pulendran's group has shed light to a novel pathway that regulates the balance between inflammatory versus tolerogenic DCs in the gut. The authors found that the Wnt-β-catenin signaling pathway is required for the expression of anti-inflammatory mediators including retinoic acid-metabolizing enzymes, IL-10 and TGF-β on intestinal DCs and the subsequent expansion of T_{reg} cells [18], suggesting that activation of the β-catenin signaling programs may be essential for driving DCs toward a tolerogenic state.

Given their remarkable plasticity and their ability to promote T-cell tolerance, administration of tolerogenic DCs has been proposed as a potential approach to prevent graft rejection and ameliorate several autoimmune disorders [14]. In fact, tolerogenic DCs contribute to the resolution of autoimmune inflammation through induction of activation-induced cell death, promotion of T-cell anergy, and/or expansion of T_{reg} cells [14,19]. These cells can be generated from myeloid precursors *ex vivo*, loaded with antigen, and manipulated to suppress autoimmune responses *in vivo* [20,21]. Alternatively, DCs may be genetically engineered to act as '*Trojan Horses*' that carry immunosuppressive mediators (e.g., TGF-β, Fas L and IL-10) that spread immune tolerance and limit exuberant inflammation [14,20,22].

In addition to their implications in self-tolerance, regulatory DCs may also play a role in fostering immunosuppression following infection with a wide array of pathogens [23,24]. In fact, microbes have evolved several evasion strategies for programming DC to become tolerogenic and induce T_{reg} cells or to amplify IL-10- or TGF-β-mediated regulatory circuits. For example, *Schistosoma mansoni* phosphatidylserine conditions DCs through TLR2 signaling to induce T_{reg} cells, while Omega-1, a *S. mansoni* glycoprotein that acts as a T2 ribonuclease, imparts a DC regulatory gene program that is critical for promoting a Th2-type cytokine profile [25,26]. In addition, the fungus *Candida albicans* signals DCs to stimulate divergent inflammatory (Th17) or T_{reg} cell responses [27]. Also, filamentous hemagglutinin (FHA) from the bacteria *Bordetella pertussis* induces DCs to produce IL-10 and prime Tr1 cells [28]. Furthermore, *Trypanosoma cruzi*, the parasite responsible of Chagas' disease, selectively instructs the differentiation of tolerogenic DCs through mechanisms involving TGF-β and IL-10 [29]. Thus, the capacity of different microbial structures to modulate DC immunogenicity or tolerogenicity might be exploited by pathogens to achieve commensalism or pathogenicity. In this regard, recent evidence revealed that intestinal DCs expressing CD103 can promote the differentiation of $Foxp3^+$ T_{reg} cells in a retinoic acid-dependent fashion [30]. Whether these cell population could be selectively expanded by different pathogens of the intestinal microbiota remains to be elucidated. Collectively, these results indicate that, while tolerogenic DCs may function to amplify regulatory circuits that limit uncontrolled inflammation, several pathogens may usurp these pathways to promote host immunosuppression. Hence, targeting regulatory signals on DCs might contribute to potentiate the efficacy of vaccination protocols.

In addition to preventing autoimmune diseases and modulating the course of infections, DCs can also influence the immunosuppressive network displayed by cancer cells [6]. Despite the fact that DCs can take-up, process, and present tumor antigens to activate a tumor-specific T-cell response, tumors actually progress, metastasize and may ultimately kill the host. Data from many laboratories obtained during the past few years indicates that defects in the DC system are one of the main factors responsible for tumor escape, which contributes in various ways to the T-cell defects in cancer and failure of immunotherapeutic strategies [6]. Alterations within the DC compartment include decreased presence of functionally competent DCs, accumulation of immature DCs and expansion of tolerogenic DCs at sites of tumor growth [6]. A multitude of factors may influence the preferential differentiation and expansion of tolerogenic DCs within tumor microenvironments including secretion of prostaglandin E2 and TGF-β [31] and selective activation of the JAK2/STAT3 pathway within the myeloid compartment [32]. However, most prominent in cancer studies are plasmacytoid DCs (pDCs) which accumulate in many tumors through mechanisms involving stromal-derived factor-1 (SDF-1) [33]. It has been shown that mouse tumor-draining lymph nodes contain a subset of pDCs that constitutively express the enzyme IDO. This may prevent the clonal expansion of T cells and promote T-cell death through tryptophan depletion [34]. Although DC-related vaccination protocols are under way in clinical trials, mounting evidence suggests that blockade of inhibitory signals or immunosuppressive pathways in the tumor microenvironment might improve the efficacy of these therapies [35]. Thus, induction of a tolerogenic or regulatory DC profile might be exploited to attenuate autoimmune diseases and prevent graft rejection. In contrast, silencing DC regulatory pathways might augment vaccination efficiency and potentiate tumor immunotherapeutic strategies.

3. Glycan recognition and signaling in DC physiology

In the postgenomic era, the study of the 'glycome' (the whole repertoire of glycans present in cells and tissues) has enabled the association of unique glycan structures with specific physiological and pathological processes [36]. The responsibility for deciphering this information belongs to endogenous glycan-binding proteins or lectins whose expression and function are regulated during the course of innate and adaptive immune responses [37]. In spite of their well-established roles in regulating cell trafficking and host–pathogen interactions, recent studies have illuminated essential functions of endogenous lectins as 'on-and-off' switches that control immune tolerance and inflammation [37]. Interestingly, a key role for DCs in inducing tolerance *in vivo* was initially noted in experiments involving targeting of glycosylated antigens into DCs through the lectin receptor DEC-205 [38]. These experiments suggested that protein–glycan interactions may serve a decisive function in the control of responsiveness and tolerance of DCs [39]. Furthermore, recent studies revealed dramatic changes in the 'glycosylation signature' of DCs during their maturation [39,40]. Bax and collegues found up-regulation of glycosyltransferases involved in the synthesis of N-acetyllactosamine (LacNAc) and sialic acid transfer but down-regulation of glycosyltransferases involved in the synthesis of core 2 *O*-glycans during DC maturation; these glycan variations led to selective binding of endogenous lectins to immature versus mature DCs [40]. Moreover, Jenner et al. found increased levels of α2,6-linked sialic acid in tolerogenic versus immunogenic DCs [41], suggesting a key role of cell surface glycosylation in regulating DC maturation and immunogenicity. Given the emerging role of lectin–glycan lattices in DC physiology, we will focus here on three receptor families (C-type lectins, siglecs and galectins) (Fig. 1) which are differentially expressed on distinct immune

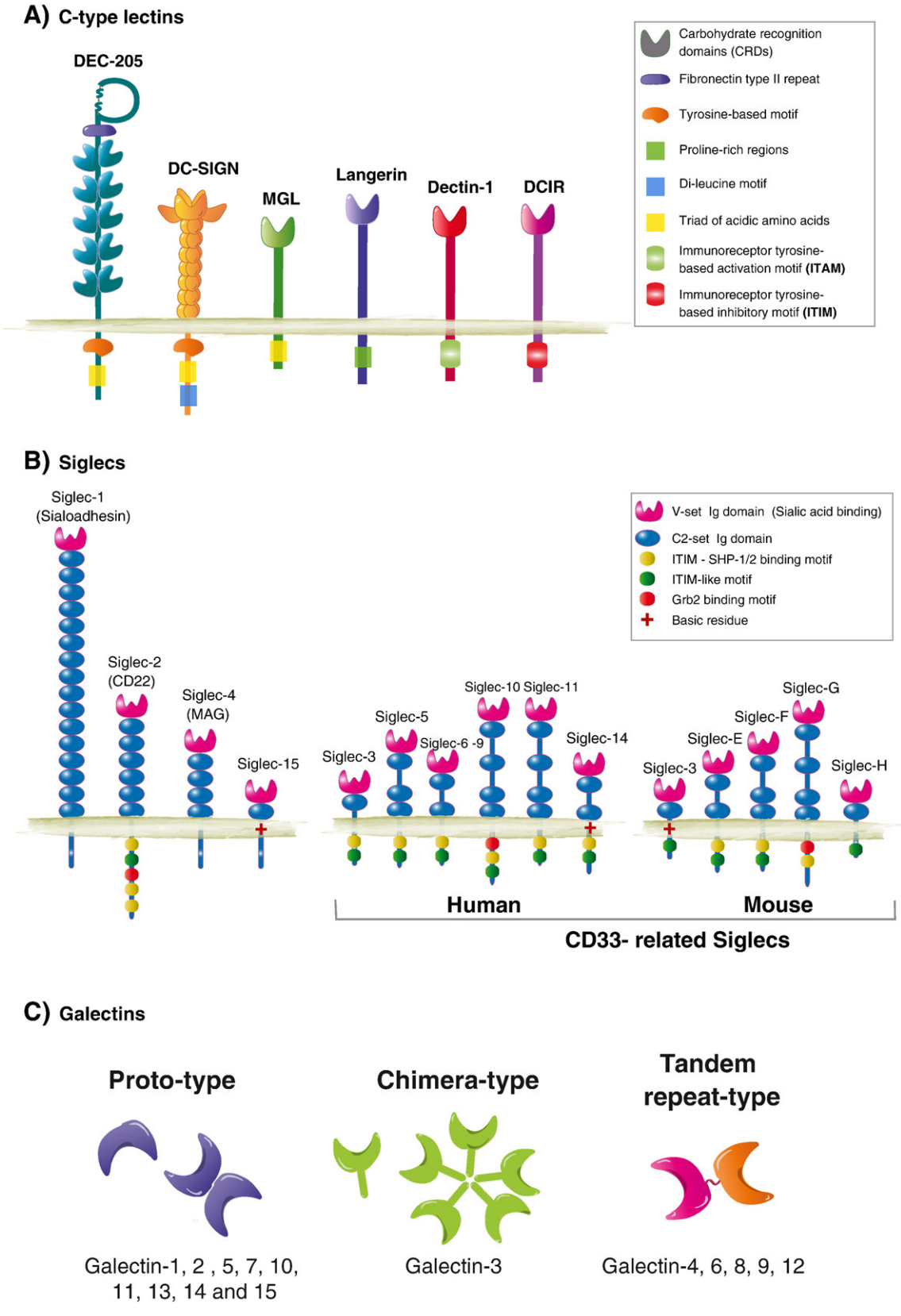

Fig. 1. Structure of members of the C-type lectin (A), siglec (B) and galectin (C) families. (A) Selected members of the broad family of C-type lectins (DC-SIGN, MGL, langerin, Dectin-1 and DCIR) expressed on DCs. (B) Siglecs are divided into sialoadhesin (Sn; Siglec-1), CD22 (Siglec-2), myelin-associated glycoprotein (MAG; Siglec-4) and the CD33-related siglecs that share high sequence similarity (Siglec-3, -5, -6, -7, -8, -9, -10, -11 and -14 in humans and Siglec-E, -F, -G and -H in mouse). (C) Based on their architecture, galectins are classified into 'proto-type', 'chimera-type' and 'tandem repeat-type'. These soluble lectins containing at least one carbohydrate-recognition domain (CRD) which can dimerize. While some members of the galectin family such as galectins-1 and -3 display broad expression profile, others such as galectins-7, -10 and -12 show a more restricted tissue distribution.

cell subsets and critically influence DC processes at the cross-road of tolerance and inflammation. While galectins are in general secreted proteins that act in a paracrine or autocrine manner, all known siglecs and most C-type lectins are membrane-bound receptors that convey glycan-containing information into DC differentiation or maturation programs [37]. Interestingly, some of the signaling pathways triggered by these different lectin families converge in similar functional outcomes regardless of divergences in their structure, homology or glycan-binding specificities.

3.1. C-type lectins

Although the role of C-type lectins as endocytic and signaling receptors is relatively well established, the function of these glycan-binding proteins in shaping DC immunogenicity is just emerging [42,43]. In fact, C-type lectin receptors (CLRs) on DCs can tailor adaptive immune responses through recognition of specific 'glycan signatures' on invading pathogens or host cells [42]. CLRs are calcium (Ca^{2+})-dependent glycan-binding proteins which can be divided into two categories on the basis of an amino acid motif involved in glycan recognition and coordination of the Ca^{2+} ion [44] (Fig. 1A). The type II subfamily of CLRs, of which 17 members have been cloned in human, is mainly restricted to APCs such as DCs, macrophages and microglia [42]. These include DC-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), L-SIGN and Langerin which share specificity for high-mannose and fucose-containing glycans ($Lewis^{a,b,x,y}$) [37]. DC-SIGN (CD209) is a type II membrane CLR that recognizes two classes of glycans, mannose-containing glycans as well as fucosylated glycans (Fucα1–3/4GlcNAc; Lewis antigens). While the best studied function of DC-SIGN is to deliver antigens to intracellular compartments to present them to naïve T cells, emerging evidence indicates an important role of this lectin in regulating immune cell tolerance [37]. Recently, Zhou et al. incorporated SIGNR1, a mouse homologue of DC-SIGN, as a new piece of the 'tolerogenic puzzle' that links exogenous food glycan structures to the activation of regulatory lamina propria DCs and to the differentiation of IL-10-producing Tr1 cells [45,46]. This study proposed that recognition of mannosylated antigens by SIGNR1 on lamina propria DCs may be crucial in triggering tolerogenic DCs [45]. Likewise, engagement of Dectin-1, a C-type lectin responsible for recognizing β-glucans on yeasts, can signal DCs either to drive the differentiation of Th17 cells or to promote the expansion of IL-10-producing tolerogenic DCs [47,48] (Fig. 2A). Similarly, engagement of P-selectin or expression of the DC immunoreceptor (Dcir) triggers inhibitory signals that limit DC functionality [49,50].

Although the molecular pathways underlying immunogenic or tolerogenic DC profiles are poorly understood, emerging studies indicate that C-type lectins can trigger divergent signaling cascades that either amplify or silence pro-inflammatory gene expression and tailor subsequent adaptive immunity [51]. For example, upon recognition of fungal β-structures, Dectin-1 triggers signaling via the Syk tyrosine kinase and activates the p38 and JNK kinase cascades and the transcription factor NF-κB to trigger pro-inflammatory cytokine responses [52]. For these signaling events, the adaptor CARD9, which forms complexes with Bcl-10 and MALT-1 is required, thus delineating a signaling pathway for this CLR [48] (Fig. 2B). Alternatively, dectin-1 in cooperation with TLR2 may instruct DCs to become tolerogenic through mechanisms involving ERK1/2 activation but independently of the AP-1 transcription factor [47]. Similar to Dectin-1, DC-SIGN can modulate either pro-inflammatory or anti-inflammatory functions through activation of alternative signaling pathways leading to positive or negative regulation of NF-κB activity [53] (Fig. 2B).

As mentioned above, pathogens have evolved several strategies to shape adaptive immunity through modulation of DC function. Recent evidence indicates that C-type lectins can mediate these subverting strategies through recognition of pathogen-associated 'glycan signatures'. In this regard, DC-SIGN serves as a signaling receptor with broad pathogen recognition specificity as a result of its affinity for mannose and fucose saccharides. Whereas high-mannose structures on the cell-wall component ManLAM of *Mycobacterium tuberculosis* target DC-SIGN to induce the synthesis of anti-inflammatory cytokines such as IL-10 [54], *S. mansoni* soluble egg antigens (SEA), expressing fucosylated (LacdiNAc)-LDN sequences and $Lewis^{x}$ or pseudo-$Lewis^{y}$ antigens in the cercaria of the parasite, target this CLR to instruct Th2 responses [55]. In an elegant study, Gringhuis and colleagues demonstrated that DC-SIGN is constitutively associated with a signalosome complex consisting of the scaffold proteins LSP1, KSR1 and CNK and the kinase Raf-1. While mannose-expressing *M. tuberculosis* and human immunodeficiency virus type 1 (HIV-1) induce the recruitment of effector proteins to the

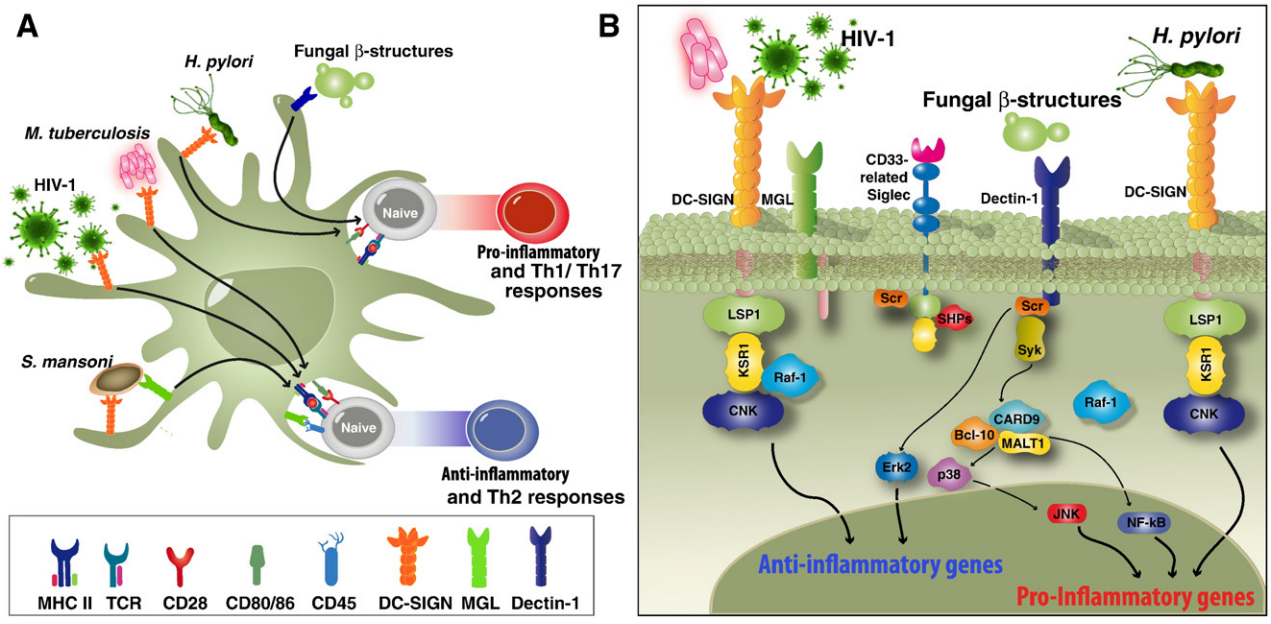

Fig. 2. Modulation of DC signaling and function by C-type lectins and siglecs. Several C-type lectins and siglecs expressed on DCs specifically recognize glycan structures found on a diversity of pathogens and tailor pro-inflammatory or anti-inflammatory responses by conveying glycan information into T cell homeostatic programs. C-type lectins can also shape the immunogenicity or tolerogenicity of APCs.

DC-SIGN signalosome to activate Raf-1, fucose-expressing pathogens such as *Helicobacter pylori* actively dissociate the Raf-1 complex from the DC-SIGN signalosome, leading to the generation of either pro-inflammatory or anti-inflammatory responses [56] (Fig. 2B). Thus, pathogens may evade immune responses by shaping the DC compartment and selectively altering adaptive immunity through glycan-mediated control of intracellular signaling pathways.

Interestingly, the C-type lectin MGL (CD301), a glycan-binding protein with restricted specificity for α- and β-linked terminal GalNAc structures is preferentially expressed on tolerogenic DCs, alternatively-activated macrophages and central nervous system microglia [43,57]. Interestingly, this rare carbohydrate preference is found in glycan moieties present in the tumor-associated mucin MUC1, in *S. mansoni* and Filoviruses or in CD45 glycoprotein on effector T cells [43]. Through binding to CD45 and altering its phosphatase activity, MGL impairs T cell signalling and inhibits pro-inflammatory cytokine secretion [43], suggesting that tolerogenic DCs can suppress T-cell activation through glycosylation-dependent interactions mediated by CD45 and MGL. In addition, it has been demonstrated that Schistosomal glycans inhibit DC maturation and induce Th2 responses through binding to MGL and DC-SIGN [55] (Fig. 2B). Thus, selective recognition of glycan structures by C-type lectin receptors may trigger divergent signaling pathways, leading to the generation of either pro- or anti-inflammatory responses in response to microbial attack or tumor growth.

3.2. Siglecs

Siglecs (sialic acid-binding immunoglobulin-like lectins) belong to the immunoglobulin superfamily and constitute the major representative members of the immunoglobulin-type (I-type) lectins [58]. They can be subdivided into two subsets: the less related group (25%–30% sequence identity) which include sialoadhesin (Sn; Siglec-1), CD22 (Siglec-2) and myelin-associated glycoprotein (MAG; Siglec-4), and the rapidly evolving group of CD33-related siglecs that share high sequence similarity (50%–99%) (Siglec-3, 5, 6, 7, 8, 9, 10, 11 and 14 in humans and Siglec-E, F, G and H in mouse) [59]. The repertoire of CD33-related siglecs varies considerably among species, with nine known siglecs in humans and only five identified in mice (Fig. 1B).

Siglecs are well known for their specificity for sialic acid-containing glycans and for their ability to discriminate among specific linkages (α2-3, α2-6 or α2-8) [58]. While sialic acid has emerged rather late in the evolution and is therefore generally absent in microbes like parasites and bacteria [60], pathogens may capture sialic acid from host cells which prevents their immune recognition as foreign and enables infection of host target cells through specific interactions with siglecs. This is the case of sialylated pathogens such as *Campylobacter jejuni*, *Neisseria meningitides* and group B *Streptococci* which interact with CD33-related siglecs [61]. While most siglecs are considered to be negative regulators of cell signaling as they contain one or more cytosolic immune receptor tyrosine-based inhibitory motifs (ITIMs), others may promote immune cell activation [58]. Remarkably, siglecs can mediate *cis* and *trans* interactions with sialylated glycans. Although in *cis* interactions the siglec is often masked by low-affinity ligands on neighboring membrane receptors, these linkages do not prevent *trans* interactions with other cell types [58]. While some siglecs have a very restricted expression pattern, others are more widely expressed within hematopoietic cells. For example, Sn is mainly expressed by macrophages, CD22 by B cells and Siglec-8 by eosinophils [58]. Interestingly, Siglec-9 and Siglec-E are selectively expressed on human and mouse myeloid-derived DCs, while Siglec-5 and Siglec-H are expressed on human and mouse plasmacytoid DCs [58]. For most CD33-related siglecs, ligand engagement results in tyrosine phosphorylation of ITIM by Src family tyrosine kinases and recruitment of Src homology 2 (SH2)-domain containing phosphatases (SHPs) such as SHP-1 and SHP-2, which control cellular activation by attenuating tyrosine phosphorylation [62] (Fig. 2B).

On the other hand, Siglec-H has been identified as a specific endocytic receptor on plasmacytoid DCs which captures viruses and other pathogens for delivery to intracellular TLRs and induction of anti-viral immunity [63]. This siglec lacks tyrosine-based signaling motifs in the cytoplasmic tail and instead associates with DAP-12, an activating molecule that mediates its function. Moreover, sialylated structures present on the protozoan *T cruzi* can interact with Siglec-E on the surface of conventional myeloid-derived DCs to trigger inhibitory signals [64]. More recently, elegant studies have identified Siglec-10 in humans and Siglec-G in mice as recognition systems capable of interacting with CD24 to discriminate between danger- and pathogen-associated molecular patterns [65]. Thus, targeting cell surface-associated siglecs might provide a novel therapeutic approach to selectively regulate inhibitory or stimulatory signals in different immune cells, including those of the myeloid cell compartment.

3.3. Galectins

In contrast to C-type lectins and siglecs which are cell surface-associated receptors, galectins are act either intracellularly through modulation of signaling pathways or extracellularly by interacting with *N*- and *O*-glycans decorating cell surface glyco-receptors [66]. These soluble lectins are mainly defined by a common structural fold and a conserved carbohydrate recognition domain (CRD) of about 130 amino acids that recognizes *N*- and *O*-glycans expressing the disaccharide N-acetyllactosamine [Galβ(1–4)-GlcNAc or LacNAc] [66]. Although galectins do not have the signal sequence required for the classical secretion pathway, most of them are secreted through a non-classical secretory pathway which is still poorly understood [67]. Some galectins (galectins-1, -2, -5, -7, -10, -11, -13, -14, -15), which are traditionally classified as 'proto-type' galectins, have one CRD that can dimerize, whereas others (galectins-4, -6, -8, -9 and -12), so called 'tandem-repeat' galectins, contain two homologous CRDs in tandem in a single polypeptide chain. Galectin-3 is unique in that it contains a CRD connected to a non-lectin N-terminal region that is responsible for oligomerization [67] (Fig. 1C). The possibility to dimerize or oligomerize and decode glycan-containing information endows galectins with the potential to mediate cell–cell communication and elicit signaling processes either through traditional receptor–ligand interactions or by establishing protein–glycan arrays—often termed 'lattices'—on the cell surface [68]. Remarkably different intrinsic and extrinsic factors may control the biological activity of galectins including: a) their regulated expression in peripheral tissues; b) the spatiotemporal remodeling of cell surface glycans generated by the concerted action of glycosyltransferases on distinct immune cell subsets; c) the dimerization or oligomerization status and d) the stability of these proteins in oxidative microenvironments [69]. Through their ability to recognize specific glycan structures on different immune cell types, galectins have been functionally linked to critical processes including host–pathogen interactions, immune cell signaling and activation, T helper cell homeostasis, preservation of fetomaternal tolerance and suppression of autoimmune pathology [68–74]. In addition, galectins contribute to create an immunosuppressive niche at sites of tumor growth and metastasis [75–77].

Although the *in vivo* role of endogenous galectins in immune tolerance is just emerging, recent studies have demonstrated unique immunological phenotypes in mice lacking individual members of the galectin family [68]. Illustrating this concept, targeted deletion of Gal-1 or Gal-9 genes (*Lgals1* or *Lgals9*) resulted in increased Th1 and Th17 responses and exacerbation of autoimmune pathology [67,78], whereas mice lacking Gal-3 gene (*Lgals3*) show reduced inflammation in mouse models of multiple sclerosis and arthritis [79,80]. Thus, in contrast to previous assumptions based on the idea of evolutionarily conservation and functional redundancy, individual members of the galectin family may have distinct functions in the regulation of

inflammatory responses. Consistent with these findings, mice lacking β-1,6*N*-glycan branch structures, which are common galectin ligands, develop a severe spontaneous inflammatory disorders that resembles progressive multiple sclerosis [71].

In search for potential mechanisms underlying these immunoregulatory effects, we studied the impact of galectin-1 in the modulation of DC physiology. We identified a hierarchy of tolerogenic signals elicited by galectin-1–glycan interactions which leads to differentiation of tolerogenic DCs [19]. When human monocytes or mouse bone-marrow progenitors were differentiated or matured in a galectin-1-enriched microenvironment, they acquired a distinctive 'regulatory signature' characterized by segregation of CD43, phosphorylation of the transcription factor STAT3, abundant secretion of IL-27 and IL-10 and induction of IL-10-producing FoxP3(−) Tr1 cells [19] (Fig. 3). More importantly, when transferred *in vivo*, these DCs promoted antigen-specific T-cell tolerance, blunted Th1 and Th17 responses and halted autoimmune inflammation through mechanisms involving DC-derived IL-27 and T cell-derived IL-10 [19]. Thus, using IL-27 receptor-deficient (*Il27ra*$^{-/-}$) and IL-10-deficient (*Il10*$^{-/-}$) mice, we have identified an immunoregulatory circuit linking galectin-1 signaling, IL-27-producing tolerogenic DCs and IL-10 secreting T_{reg} cells. Interestingly, pro-inflammatory or Th1-polarizing stimuli induced a considerable reduction of galectin-1 expression on DCs, while tolerogenic or Th2-polarizing stimuli, such as *S. mansoni* egg antigen (SEA), VIP or apoptotic cells, selectively up-regulated expression of this lectin through intracellular pathways involving ERK1/2 and JNK [19]. In accordance with its regulatory function, bone marrow-derived or splenic DCs from *Lgals1*$^{-/-}$ mice showed an enhanced immunogenic capacity in both *in vitro* and *in vivo* settings [19], suggesting a critical role of endogenous galectin-1 in 'fine-tuning' the immunogenicity of DCs. Most recently, the tolerogenic activity of galectin-1 was confirmed in tumor settings. Kuo and colleagues found that lung cancer-derived galectin-1 altered the phenotypes of monocyte-derived DCs, impaired alloreactive T cell response and increased the frequency of FoxP3^{+} regulatory T cells. The authors demonstrated that these regulatory effects were, at least in part, mediated by activation of the transcription factor Id3 (inhibitor of DNA binding 3) and the secretion of IL-10 [77]. Furthermore, injection of recombinant galectin-1 favored the recruitment of a subset of uterine DCs with a tolerogenic phenotype [81]. On the other hand, other studies demonstrated that exposure to galectin-1 promoted the maturation and migration of DCs through mechanisms involving Syk and PKC signaling [82] (Fig. 3). The authors showed that galectin-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 galectin-1 increased the *in vivo* migration of dermal DCs to draining lymph nodes [82], suggesting that DCs exposed to galectin-1 may acquire a distinctive immunomodulatory program characterized by either a 'mature' or an 'immature' cell surface phenotype, but increased migration profile and enhanced tolerogenic potential. A possible explanation for these apparent discrepancies could be a bifunctional role of galectin-1 acting as a tolerogenic mediator at relatively low concentrations (0.3–3 μM), while displaying immunogenic signals when secreted at high levels (20 μM) from damaged cells. Nevertheless, we might also hypothesize that, in the presence of galectin-1, DCs may undergo maturation and migrate to second lymphoid organs to promote T-cell tolerance, thus integrating different functions of this lectin.

Similarly, DCs lacking galectin-3 secrete higher amounts of IL-12 than wild-type DCs and favor the polarization of T cells toward a Th1-type profile [83,84], suggesting a common mechanism by which endogenous galectins may control DC immunogenicity. In addition, endogenous galectin-3 can also regulate the trafficking pattern of DCs through intracellular mechanisms involving control of membrane ruffles [85]. Although the effect of exogenous galectin-3 has not been examined in such detail, a recent work suggested that this 'chimera-type' lectin binds with lower affinity to immature and mature DCs compared to human monocytes [86]. Partridge and colleagues proposed a general glycosylation-dependent mechanism by which galectin-3 cross-linking to complex *N*-glycans on cytokine receptors may delay their surface removal by endocytosis and promote sustained cytokine signaling by leukocytes [87], thus providing an alternative function for this immunoregulatory lectin. In addition, ligation of Tim-3, a specific receptor for galectin-9, induces divergent functions on APCs and T cells leading to initiation or termination of Th1-dependent immunity [88] (Fig. 3). In fact, DCs exposed to galectin-9 produce higher levels of IL-12 and are endowed with Th1-polarizing capacity [89]. Interestingly, both galectins-1 and -3 promote the differentiation of 'alternatively-activated' macrophages

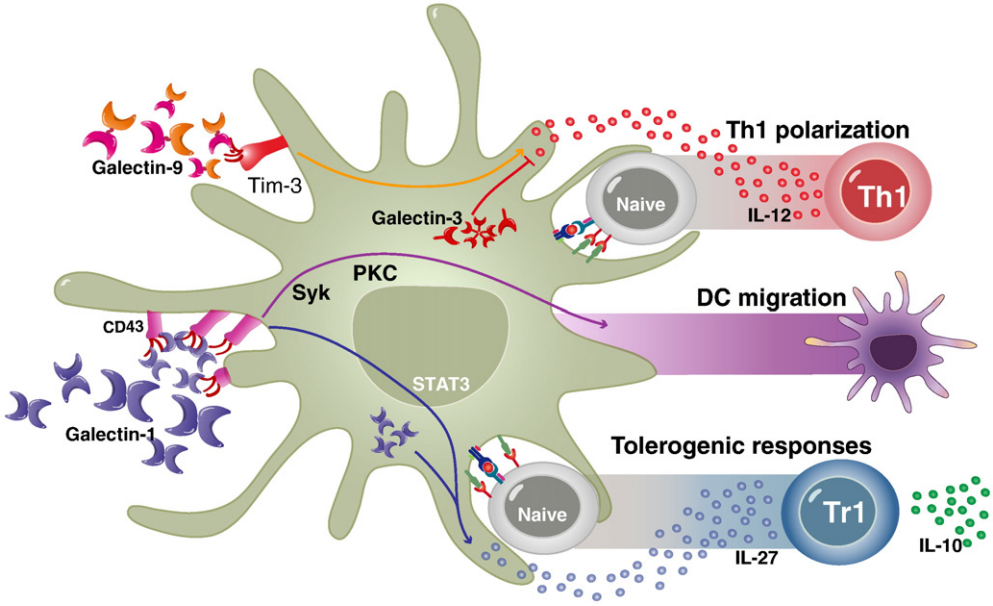

Fig. 3. Modulation of DC signaling and function by galectins. Galectins modulate a variety of signaling pathways to trigger the maturation, immunogenicity and migration of DCs. While galectin-1 activates a cascade of inhibitory events leading to the amplification of a tolerogenic circuit mediated by IL-27 and IL-10, it also promotes DC maturation and migration through mechanisms mediated by the CD43 glyco-receptor. Endogenous galectin-3 inhibits IL-12 production, whereas galectin-9 induces DC maturation and Th1-type cytokine polarization through engagement of Tim-3.

via activation of ERK1/2 or PI3K respectively similar to their regulatory effects on DCs [90–92]. Thus, galectin–glycan lattices may have evolved to regulate APC homeostasis and control their activation and signaling.

4. Conclusions and future perspectives: capitalizing on lectin–glycan interactions for the design of DC-based immunotherapeutic strategies

Here we summarized emerging evidence on the role of three different families of glycan-binding proteins (C-type lectins, siglecs and galectins) in 'fine-tuning' the immunogenic or tolerogenic function of DCs. While cell surface-associated CLRs such as DC-SIGN, Dectin-1 and MGL convey extracellular glycan information into DC immunogenic or tolerogenic programs, most siglecs act as negative regulators of cell signaling through activation of ITIMs and soluble galectins (e.g. galectins-1, -3 and -9) cross-link DC surface glycoconjugates to transduce stimulatory or inhibitory signals. Because DCs are pleiotropic modulators of T-cell activity and are endowed with exquisite plasticity, manipulation of their function to favor the induction of DCs with immunogenic or tolerogenic properties could be selectively exploited to positively or negatively regulate immune responses in order to potentiate vaccination and cancer immunotherapeutic strategies, suppress autoimmunity and prevent graft rejection [3]. However, before lectin-based therapeutic strategies can be fully realized there is still much to be learned concerning the contribution of glycan specificity, the nature and relevance of protein–glycan lattices *in vivo*, and the cross-talk among different lectin families in the amplification, silencing or tuning of inflammatory responses. These unresolved issues together with the lack of reliable methods to measure lectin–glycan interactions *in vivo* have significantly hindered translation of glycan-containing information into biotechnological and pharmaceutical applications. Yet, innovative technologies including lectin microarrays, glycan visualization *in vivo* and frontal affinity chromatography, as well as the generation of gene-deleted mice devoid of endogenous lectins or glycosyltransferases [93–95] are rapidly changing the scene and creating novel opportunities for capitalizing on the information encoded by the 'glycome' for therapeutic purposes.

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