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Shedding light on the immunomodulatory properties of galectins: Novel regulators of innate and adaptive immune responses

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Galectins are a large family of structurally related β-galactoside-binding proteins that play a pivotal role in the control of cell differentiation, proliferation, activation and apoptosis of many different cell types including immune cells. By crosslinking specific glycoconjugates, different members of the galectin family behave as pro-inflammatory or anti-inflammatory "cytokine-like" mediators, acting at different levels of innate and adaptive immune responses. Here we will review recent advances on the role of galectins in key events of the immune and inflammatory response, such as tolerance induction, cell cycle progression, cell adhesion, chemotaxis, antigen presentation and apoptosis. In particular we will examine the influence of individual members of the galectin family in the physiology of different immune cell types involved in innate and adaptive immune responses. Moreover, we will discuss the importance of these sugar-binding proteins as therapeutic targets in Th1- and Th2-mediated immune disorders, an exciting area for future research.
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Abbreviations: **Con A: concanavalin A; CRDs: carbohydrate recognition domains; ECM: extracellular matrix; Gal: galectin; IFN-γ: interferon-γ; LPS: lipopolysaccharides; Mϕs: macrophages; PHA: phytohemagglutinin; TNF-α: tumor necrosis factor-α.**

Introduction

Galectins are animal lectins defined by shared consensus amino acid sequences and affinity for β-galactose-containing oligosaccharides [1–4]. This is an evolutionarily highly conserved family and homologues exist in mammals as well as in lower organisms such as nematodes, sponges and even in microorganisms [1,3]. In mammals, fourteen members have been reported and a large number of additional members are identifiable in the published databases [1]. Members are composed of one or two carbohydrate-recognition domains [CRDs] of approximately 130 amino acids [1]. The definition, structure, saccharide specificity and biochemical properties of this growing family of animal lectins are clearly presented in previous chapters of the present issue.

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Galectins are present in different immune cell types such as T cells [5–8], B cells [9], macrophages [10–13], eosinophils [14,15], basophils [14] and thymic epithelial cells [16]. Moreover, galectin expression is modulated by different inflammatory stimuli according to the activation state of these cells [8–13].

Here we will review the pleiotropic effects of galectins in the physiology of different immune cell types during innate and adaptive immune responses (Figure 1) and their participation in acute and chronic inflammatory disorders (Table 1).

Immunomodulatory properties of galectins: A lesson from autoimmunity and T cell-mediated chronic inflammation

The inflammatory response involves the sequential release of mediators and the recruitment of circulating leukocytes. This response is self-limited and resolves through the release of endogenous anti-inflammatory cytokines and other mediators. Current approaches for the treatment of inflammation rely on the inhibition of pro-inflammatory mediators and the identification of novel molecular targets for anti-inflammatory drugs.

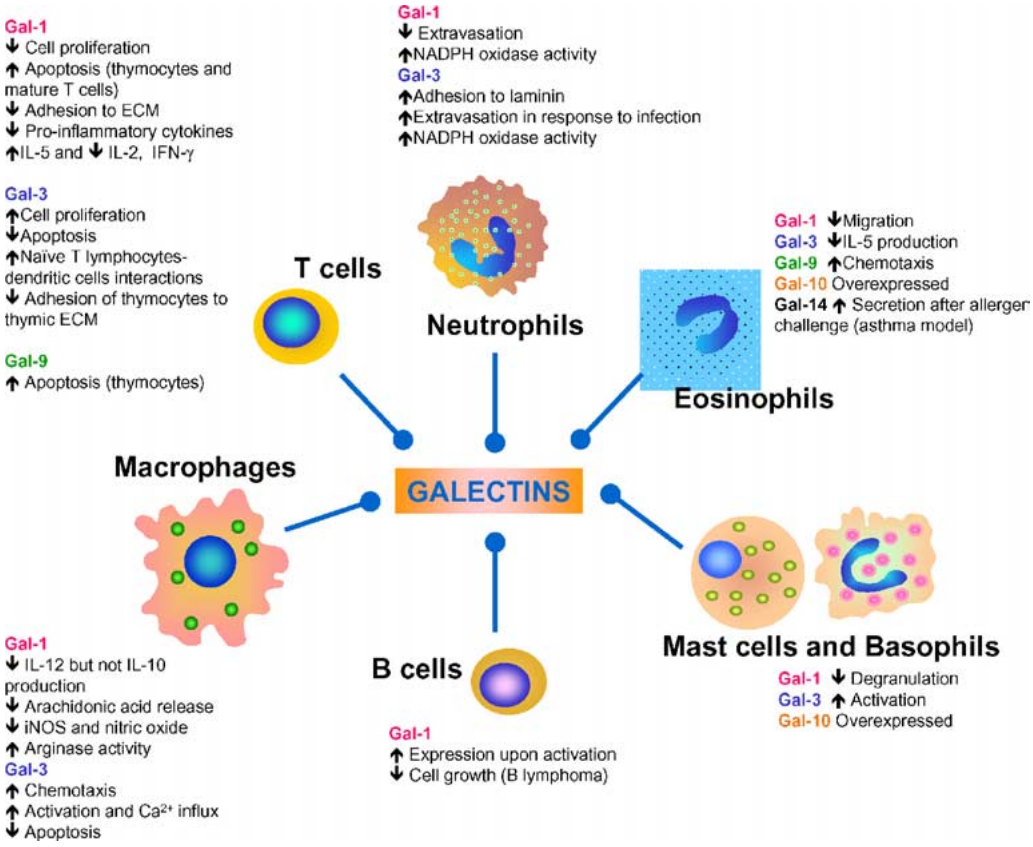

Figure 1. Effects of galectins in the physiology of several immune cell types involved in innate and adaptive immune responses.

A growing body of experimental evidence indicates that galectins may play a key role in the initiation or resolution of chronic and acute inflammatory processes [17–20]. Whereas some members of this protein family act in the resolution of inflammatory responses, it is intriguing that other members with similar carbohydrate specificity and conserved amino acid sequence may contribute to the initiation and amplification of the inflammatory response [3]. However, it was recently realized that the same galectin may exert pro- or anti-inflammatory effects depending on multiple factors, such as the concentration and the target cell tested. It has been suggested that multivalency of individual members of the galectin family and their crosslinking properties might determine different biological responses by inducing aggregation of specific cell surface glycoreceptors, which in many cases, are associated with different signal transduction events [21].

Galectin-1, a proto-type member of the galectin family, has been proposed to be, in general, a negative regulator of the immune response [3]. This β-galactoside-binding protein suppresses cell growth [5,22–24], inhibits T cell-matrix interactions [25] and induces T cell apoptosis [11,24,26,27]. *In vivo*, this β-galactoside-binding protein prevents the development of chronic inflammation and ameliorates the ongoing disease in experimental models of autoimmune encephalomyelitis [19], arthritis [17], hepatitis [18] and colitis [28] (Table 1). We have recently demonstrated using gene and protein therapy strategies that galectin-1 suppresses the chronic inflammatory response in collagen-induced arthritis in DBA/1 mice, an

Table 1. Modulation of chronic inflammatory disorders by galectins

T cell-mediated	Experimental autoimmune encephalomyelitis (EAE) in Lewis rats	Gal-1
	Collagen-induced arthritis (CIA) in DBA/1 mice	
	Con A-induced hepatitis in BALBc mice	
	TNBS-induced colitis in BALBc mice	
Autoantibodies-mediated	Experimental autoimmune myasthenia gravis (EAMG) in New Zealand rabbits	Gal-1 homologue
	Experimental nephrotoxic nephritis induced by anti-basement membrane antibodies in Wistar Kyoto rats	Gal-1
		Gal-3
		Gal-9

experimental model of rheumatoid arthritis [17]. Injections of fibroblasts genetically engineered to secrete galectin-1 or continuous administration of recombinant galectin-1 after the onset of the disease abrogated clinical and histopathological manifestations of arthritis [17]. Dissection of the cellular and molecular mechanisms involved in these anti-inflammatory effects, revealed that lymph node cells from galectin-1-treated mice were more susceptible to antigen-induced apoptosis [17]. Moreover, galectin-1 treatment induced a shift from a Th1 towards a Th2-polarized immune response, characterized by decreased IFN-γ and IL-2 secretion and increased IL-5 production by lymph node cells. Whether this effect is only the result of increased T-cell apoptosis or whether different mechanisms operate to achieve immunosuppression is an issue under current investigation. The inhibitory effect of galectin-1 was also reflected by the reduced-IL-2 production by a collagen-type II-specific T-cell hybridoma clone cultured in the presence of antigen presenting cells, collagen-type II and galectin-1-transfected fibroblasts [17]. Interestingly, we found that synovial tissue from patients with juvenile rheumatoid arthritis (JIA) have significantly less galectin-1, but more galectin-3 than normal sinovial tissue [29]. This regulated expression correlated with decreased mononuclear cell apoptosis in synovial tissue from these patients. The immunosuppressive activity of galectin-1 has been also demonstrated in concanavalin A (Con A)-induced hepatitis a T-cell dependent model of liver injury in mice, characterized by the presence of infiltrating T cells in the liver [18]. Galectin-1 prevented both liver injury and T-cell infiltration induced by Con A, an effect associated with selective elimination of Con A-activated T cells and suppression of Con A-induced TNF-α and IFN-γ production [18]. Furthermore, Santucci and colleagues [28], recently confirmed these findings in Th1-mediated experimental colitis, an inflammatory bowel disease induced by intrarectal administration of 2,3,4-trinitrobenzene sulfonic acid (TNBS) in mice, demonstrating a striking improvement in the clinical and histopathological aspects of the disease after prophylactic and therapeutic administration of galectin-1, with increased apoptosis of mononuclear cells *in vivo*.

In addition to its role in Th1-mediated inflammatory processes, galectin-1 might also play a role in autoantibody-mediated chronic inflammation since a galectin-1 homologue purified from the fish *Electrophorus electricus* was able to prevent the development of experimental myasthenia gravis (EAMG) in rabbits [30]. Furthermore, galectin-1, -3 and -9 were also tested for their ability to modulate the progression of nephrotoxic nephritis induced by injection of anti-glomerular basement membrane serum in Wistar Kyoto rats [31]. Notably, T cell apoptosis was not evident in this system, suggesting that alternative mechanisms might indeed operate to achieve a therapeutic and anti-inflammatory effect. Interestingly, the presence of anti-galectin autoantibodies has been identified in several autoimmune and inflammatory disorders, such as neuropathies [32], Chagas' cardiomiopathy [33], Crohn's disease [34] and systemic lupus erythematosus [35], suggesting that they might play a role in the pathogenesis of autoimmune disease.

In addition to the role of galectin-1 in inflammatory responses, galectin-3 appears to be a positive regulator of inflammation. As will be discussed in detail in next sections, galectin-3 promotes cell adhesion [36], prevents T-cell apoptosis [37], attracts leukocytes [38] and promotes activation of a basophil cell line *in vitro* [39]. Studies *in vivo* have provided significant support for the proinflammatory role of this lectin [40, 41]. Targeted mutation of the galectin-3 gene resulted in less inflammatory cells after induction of peritonitis by injection of thyoglicolate [41]. In addition, inflammatory peritoneal cells from galectin-3-deficient mice showed significantly reduced levels of NF-κB activation [41].

To gain insight into the molecular basis of the immunomodulatory properties of galectins, we will summarize the effects of these proteins in the physiology of several cell types involved in innate and adaptive immune responses.

Molecular basis of the immunomodulatory properties of galectins: Modulation of T cell physiology

Investigation of the cellular and molecular mechanisms involved in the immunomodulatory properties of galectins revealed that extracellular galectin-1 induces cell growth inhibition, cell cycle arrest and apoptosis of activated, but not resting T cells [5,11,22,23,26].

Galectin-1 showed specific growth inhibitory properties towards Con A-stimulated rat T cells [22], PHA-activated human T cells [5], chicken activated T cells [42], human leukemia T cell lines [24] and human alloreactive T cells [7]. Further investigation revealed that galectin-1 induces apoptosis of peripheral T lymphocytes and developing thymocytes [11,22,26,27,43]. It has been shown that galectin-1 promotes apoptosis of immature cortical thymocytes *in vitro*, suggesting a potential role for this carbohydrate-binding protein in the maintenance of central tolerance [43]. In addition, galectin-1 kills preferentially fully activated T cells [26]. Similarly to galectin-1, mouse galectin-9 also induces apoptosis of thymocytes, in a lactose-inhibitable fashion [44].

Different cell surface glycoconjugates appear to be primary receptors for galectin-1, such as CD45, CD43, CD2, CD3 and CD7 [42,45–48]. Interestingly, galectin-1 binding to T cells results in a marked redistribution of these glycoproteins into segregated membrane microdomains [47]. Furthermore, Nguyen *et al.* [49] have recently demonstrated that CD45 can positively or negatively regulate galectin-1-induced T cell death, depending on the glycosylation status of the cells. Hence, $CD45^+$ T cells lacking the core 2 beta-1,6 *N*-acetylglucosaminyltransferase (C2GnT) are resistant to galectin-1 death. This enzyme is responsible for creating branched structures on *O*-glycans of T-cell surface glycoproteins such as CD45 [49,50]. Recent studies confirmed that T-cell susceptibility to galectin-1-induced cell death, is regulated by

the balance of at least two glycosyltransferases. While C2GnT is necessary for galectin-1 to promote apoptosis [50], the ST6Gal I syalyltransferase selectively modifies *N*-glycans on CD45 to negatively regulate T-cell death [50,51]. Moreover, galectin-1 up-regulates the expression of both the α- and β-chains of IFN-γ receptor on activated T lymphocytes and the increased expression of both chains renderes the cells more susceptible to IFN-γ-induced apoptosis [23]. On the other hand, CD7 has been identified as a critical receptor for galectin-1-induced apoptosis [48] and it has been recently revealed that $CD4^+$ $CD7^-$ leukemic T cells from patients with Sezary syndrome are protected from galectin-1-triggered T cell death [52].

Investigation of the intracellular signals involved in galectin-1-induced apoptosis revealed activation of the AP-1 transcription factor [27], downregulation of anti-apoptotic Bcl-2 [24,27], and activation of extracellular signal regulated kinase-2 (ERK-2) activation [53]. Moreover, Chung *et al.* [54] reported that this lectin antagonizes IL-2 production by inducing partial TCR-ζ chain phosphorylation.

Taking together, all these exciting findings suggest that galectin-1 might play an important role in T-cell tolerance and homeostasis *in vivo*. However, targeted disruption of the galectin-1 gene in knock out mice results in the absence of major phenotypic abnormalities (no evident changes at the level of thymic selection and no spontaneous autoimmune or inflammatory disorders) [55]. These findings suggest that other proteins (probably members of the galectins family) might potentially compensate for the absence of galectin-1, as has been shown for null mutations in ostensibly important genes. However, a careful examination of the immune physiology of these mice and their response to different inflammatory stimuli or exposure to pathological conditions (infection, autoimmunity or cancer) will be required to assign a definitive role for this sugar-binding protein in the maintenance of central and peripheral tolerance.

While the major mechanism responsible for the immunosuppressive properties of galectin-1 seems to be the induction of T-cell apoptosis, we have recently demonstrated using a human allogeneic T-cell model that alternative mechanisms may operate to achieve T-cell hyporesponsiveness and immunosuppression, as demonstrated by selective inhibition of Th1 cytokine production in the viable non-apoptotic T cell population [7]. Moreover, at concentrations lower than 4 μg/ml galectin-1 inhibits T-cell adhesion to extracellular matrix (ECM) glycoproteins such as fibronectin and laminin and abrogates the production of proinflammatory cytokines, such as TNF-α and IFN-γ by activated T cells, while does not induce T cell apoptosis [25]. Since different functions have been reported for galectin-1 according to the concentrations used in the different studies, a hypothetical model could be proposed in which this protein is secreted in low physiological concentrations from immunocompetent or stromal cells after the completion of an inflammatory or immunological response. The presence of active galectin-1 in the extracellular milieu would contribute to block proinflammatory and Th1 cytokine production and to negatively regulate T-cell adhesion to ECM as a compensatory mechanism. Furthermore, if this first regulatory mechanism is not sufficient to achieve immunological homeostasis, enhanced secretion of galectin-1, together with prolonged stimulation and persistence in the extracellular milieu, would finally induce apoptosis of activated T cells.

It should be mentioned that galectin-1 is a dynamic molecule undergoing monomer-dimer equilibrium (Kd $\sim$ 7 μM). This equilibrium is highly dependent on the concentration of the lectin and its interactions with glycoconjugates in the extracellular space. Since galectin-1 has been demonstrated to crosslink glycoconjugates and initiate signal transduction events at high concentrations, there was an assumption that only the dimeric form of this protein (which is abundant at these high concentrations) was able to exert biological effects. However, recent findings indicate that lower concentrations of this protein are also able to modulate cellular functions [12,20,25], suggesting that galectin-1 might also have biological activity in its monomeric form. It still remains to be investigated whether these functions involve carbohydrate-dependent or independent interactions.

Several studies have also reported a critical role for galectin-3 in T cell survival and proliferation and many of them indicate an anti-apoptotic effect of this β-galactoside-binding protein. However, it should be highlighted that most of the work done was focussed on the intracellular functions of galectin-3, while the proapoptotic effects of galectin-1 have been assessed using exogenous recombinant galectin-1. In the future, experiments should be conducted to examine in parallel the effects of extracellular addition of galectins-1 and -3 and to perform an exhaustive analysis of the intracellular functions of both lectins.

The first evidence indicating that galectin-3 may play a role in T cell survival was the observation that human leukemia T cells transfected with galectin-3 cDNA showed higher rates of proliferation and were protected from apoptosis induced by a wide variety of pro-apoptotic stimuli [37]. Moreover, inhibition of galectin-3 by an oligonucleotide antisense, specifically inhibited proliferation of anti-CD3-stimulated T cells [6]. It should be highlighted that galectin-3 also prevents apoptosis induced by nitric oxide and death triggered by loss of cell anchorage (anoikis) in tumor cells [56,57]. An examination of the mechanisms responsible for this effect revealed that galectin-3 acts by preventing alterations of the mitochondrial membrane and formation of reactive oxygen species [58]. Moreover, recent observations also indicate that post-translational modifications such as galectin-3 phosphorylation are essential for its anti-apoptotic activity [59].

Recently, an interesting finding was reported by Demetriou *et al.* [60] who suggested that galectin-3 might play a potential role in restricting recruitment of the T cell receptor (TCR) complex to the site of antigen presentation. The authors generated knock out mice for *Mgat-5*, a key enzyme in the glycosylation pathway of T cells. These animals showed increased delayed type hypersensitivity (DTH) responses *in vivo* and an increased susceptibility to autoimmune disorders. The assumption made

by the authors was that galectin-3 forms multivalent lattice with glycoproteins of the TCR and thereby restrains the lateral mobility of TCR complexes. Hence, in *Mgat-5* deficient mice, dysregulation of galectin-glycoproteins associations may increase TCR activation and susceptibility to autoimmune disease [60]. The model predicts that in *Mgat5* null T cells, mobility restraints imposed by "galectin-glycoprotein lattices" are relieved, because deficiency of the Mgat5-dependent β1-6 branches does not allow galectin-3 (or other galectins) to effectively engage TCR-associated glycans. Although this study demonstrated the presence of immunoreactive galectin-3 in these lattices, the large number of galectins and other lectins that may interact with N- and O-glycans, amplifies the potential for complexity in this system. Mice with deletions of the galectin-3 and -1 loci have not been reported to experience autoimmunity [55] and the biology of the TCR complex in these mice has not yet been closely examined. Therefore, future studies should be required to clarify these issues.

Regarding a role of galectin-3 in cell-cell and cell-matrix interactions, some opposing studies have also been reported. While galectin-3 has been shown to positively contribute to cell interactions between dendritic cells and naïve T lymphocytes in T cell dependent areas of lymph nodes [61], a recent study revealed that intrathymically-produced galectin-3 disrupts thymocyte interactions with the microenvironment, thus acting as a de-adhesion molecule [62].

Although there is still no evidence of their role within the immune system, other members of the galectin family have been also shown to modulate cell adhesion and survival, being examples, galectin-7, which increases susceptibility of keratinocytes to UVB-induced apoptosis [63], galectin-8 which modulates tumor survival by binding to β-integrins [64] and galectin-12 that modulates cell cycle progression and apoptosis in adipocytes [65].

Galectins and B cell physiology

Although consistent evidence has been obtained regarding the effects of galectins in T cell function, less is known about the role of these proteins within the B-cell compartment (Figure 1). Recent findings highlighted a role for galectin-1 as a stromal cell ligand of the pre-B cell receptor (BCR) implicated in synapse formation between pre-B and stromal cells [66]. Moreover, galectin-1 is expressed on activated, but not resting B cells and its expression is dramatically up-regulated by cross-linking of the BCR and the costimulatory molecule CD40 [9]. While primary cultures of B lymphocytes were not susceptible to the apoptotic effect of galectin-1 as were T cells [9], other studies showed that galectin-1 inhibits cell growth and modulates signalling in B lymphoma cell lines [46,67]. This finding is relevant to the difference between non-transformed antigen-stimulated B cells and transformed B-cell lines. Because galectins also modulate autoantibody-mediated chronic inflammatory disorders [17,30,31], further investigation should be focussed on the role of galectins in B-cell physiopathology.

Galectins in acute inflammatory processes

In addition to the role of galectins in chronic inflammatory disorders, these sugar-binding proteins also modulate acute inflammatory processes [20,40,41]. We have demonstrated that galectin-1 inhibits bee venom phospholipase A_2-induced edema in a selective and dose-dependent manner, when pre-injected or co-injected together with the enzyme [20]. In contrast to the anti-inflammatory effects of galectin-1, studies of induction of peritonitis in galectin-3-deficient mice provided significant support for the proinflammatory role of this lectin [40,41].

Influence of galectins on monocyte/macrophage physiology

Monocytes/macrophages (Mϕs) are important effector cells, which play central roles during innate and adaptive immune responses (Figure 1). Thus, expression and function of galectins have been studied in different populations of peripheral blood monocytes and peritoneal Mϕs [10–13]. Expression of galectins-1 and -3 has been found to be regulated by a wide variety of stimuli, such as thioglycolate, lipopolysaccharides [LPS], IFN-γ, phorbol esters, calcium ionophores and formylated peptides [FMLP] in resident, inflammatory and activated macrophages [10,11,13,41,68]. Moreover, galectin-3 expression significantly increased as human monocytes differentiated into macrophages upon culturing *in vitro* [68].

To study the effect of galectin-1 on the microbicidal activity of Mϕs, we used *Trypanosoma cruzi* infection as a model of intracellular infection [12]. Exogenously added galectin-1 induced a biphasic modulation of parasite replication and cell survival in Mϕs isolated from *Trypanosoma cruzi*-infected mice or in Mϕ cell lines infected *in vitro* with living trypomastigotes [12]. While low concentrations of this protein increased parasite replication and did not affect cell survival, high inflammatory doses of galectin-1 promoted macrophage apoptosis and decreased the number of intracellular amastigotes and extracellular trypomastigotes [12]. Interestingly, low concentrations of this sugar-binding protein were sufficient to downregulate critical mediators for parasite killing such as IL-12 and nitric oxide, while did not affect IL-10 production. In this context, we have also shown that galectin-1 prevents arachidonic acid release and prostaglandin E_2 production by LPS-stimulated macrophages [20]. Moreover, a recent study revealed that this protein modulates alternative pathways of L-arginine metabolism in rat peritoneal Mϕs by inhibiting inducible nitric oxide synthase (iNOS) activity and promoting activation of the arginase pathway [69].

On the other hand, galectin-3 potentiates different Mϕ functions, such as LPS-induced IL-1 production [70] and acts as a potent chemoattractant for human monocytes [38]. The chemotactic activity of galectin-3 is inhibited by pertussis toxin [PTX], suggesting that a G-protein coupled receptor may be involved in this process. In addition, galectin-3 induces Ca^{2+} influx in monocytes that is inhibitable by lactose [38]. Furthermore, peritoneal Mϕs from galectin-3 knock out mice displayed higher

levels of apoptosis, compared to cells from wild type mice, suggesting that this sugar-binding protein also protects Mϕs from cell death [41].

Influence of galectins on neutrophil physiology

Neutrophils play a key role in the innate immune response to infection and are activated by inflammatory mediators produced by microorganisms and host inflammatory cells (Figure 1). Galectin-1 inhibited neutrophil extravasation in a model of acute inflammation using the rat paw edema test [20]. Interestingly, the paradigm of "anti-inflammatory" galectin-1 and "pro-inflammatory" galectin-3 has been recently challenged in polymorphonuclear neutrophils [71]. Karlsson and colleagues [71,72] showed that both lectins increase the activity of superoxide-producing NADPH-oxidase at similar levels in primed neutrophils, providing experimental evidence of a proinflammatory effect for galectin-1.

In addition to the role of galectins in activating the respiratory burst, galectin-3 has been shown to modulate neutrophil adhesion to laminin [36]. Moreover, recent findings showed that galectin-3 is up-regulated in endothelial cells during *Streptococus pneumoniae* infection [73] and that this protein promotes neutrophil adhesion to endothelial cells *in vitro*, suggesting a potential role for galectin-3 in neutrophil β-integrin-independent extravasation.

Influence of galectins on eosinophils, basophils and mast cell functions

Eosinophils, basophils and mast cells are key effector cells during Th2-mediated allergic reactions (Figure 1). Galectin-3 was first reported as an IgE-binding protein (so called εBP) able to interact with some IgE glycoforms [39]. Whilst galectin-1 promoted a shift towards a Th2-cytokine profile [17], galectin-3 has been shown to downregulate IL-5 gene expression on eosinophilic cell lines and allergen-specific T cells [74]. On the other hand, galectin-1 has been recently shown to inhibit eosinophil migration *in vitro* [75].

Interestingly, galectin-9 (ecalectin), secreted by antigen-stimulated T lymphocytes, has been identified as a potent eosinophil-specific chemoattractant and a novel eosinophil activating factor [8]. Moreover, the Charcot Leyden crystal protein (CCL-10) or galectin-10 is highly expressed in human eosinophils and basophils, suggesting a potential role for this protein in allergic reactions [14]. Most recently, Dunphy and colleagues [15] have recently identified a novel eosinophil-specific galectin (galectin-14) released into the lumen of the lung in response to allergen challenge in a sheep asthma model. Moreover, Zuberi and colleagues [39] studied the effect of galectin-3 in basophils and mast cell activation *in vitro*, using rat basophilic leukemia (RBL) cells as a model system. The authors concluded that under appropriate conditions, this protein might have the potential to activate and degranulate these cells, culminating in augmentation of an inflammatory response. Finally, in a model of acute inflammation (rat paw edema test) galectin-1 treatment inhibited degranulation of tissue mast cells [20].

Conclusion and future perspectives

The evidences presented here illustrate the importance of different members of the galectin family in the regulation of innate and adaptive immune responses. This growing family of endogenous lectins play important roles in cell growth regulation, activation, cell adhesion, cytokine production, chemotaxis and apoptosis. However and despite considerable progress in elucidating galectin functions within the immune system, future comparative studies among different galectins will be necessary to address the precise role of individual members of the family and their functional redundancy. Future work should be conducted to elucidate the precise mechanisms implicated in the immunomodulatory properties of these protein family at the cellular and molecular levels and to examine carefully the immune system of galectin knock out mice and their response to different inflammatory stimuli.

Regarding the potential use of galectins or its inhibitors as therapeutic targets in inflammatory processes, future studies should be aimed at examining the toxicity of these sugar-binding proteins or their glycomimetics, their tissue distribution, pharmacokinetics and tolerable doses. This information will contribute to delineate novel therapeutic strategies in autoimmune, inflammatory, allergic and neoplastic diseases.

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