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Galectins in parasite infection and allergic inflammation

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Galectins are increasingly recognised as important immunological mediators of homeostasis and disease regulation. This paper gives an overview of current knowledge of galectin involvement in parasite infection and allergic inflammation, two very different but immunologically linked phenomena. Galectins are produced by both the parasite and the host and appear to be intimately involved in parasite establishment, as well as directing the course of infection and the immune response. Host galectins have also been shown to be active participants in the recruitment of cells to sites of inflammation and modulating the effector function of mast cells, neutrophils and eosinophils. Moreover, the ability of galectins to induce differential expression of cytokine genes in leukocytes suggests that they are able to direct the nature of an adaptive immune response, in particular towards a T2-type allergic response.
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Introduction

Parasitology encompasses a variety of eukaryotic pathogens, including protozoal parasites, helminth (worm) parasites and ecto (insect) parasites. Of significance to the present review is that the host response to the different parasitic organisms can be extremely diverse and often antagonistic. In particular, the cell-mediated response usually required for protection against single cell organisms is very different from the immune response that protects against the multicellular helminth and insect parasites, and induction of the inappropriate response can exacerbate an infection. The nature of these different types of immune responses has now been defined at the molecular level with the discovery of cytokines, and include T1-type (IL-12, IFN-γ, IL-2, macrophage activation) or T2-type (IL-4, IL-13, IL-5, IL-10, eosinophils, mast cells, IgE) immune responses [1]. It is the latter, T2- type response, typical for helminth parasite infections, that is of particular interest to the present review.

The immune, T2-type response elicited by helminth parasite infections is very similar to the allergic response, in that they share the same primary effector cells (mast cells, basophils and eosinophils) and usually involve induction of an 'atopic' IgE antibody isotype response [2,3]. Indeed, it has been suggested that allergic responses represent a misdirected activation of the arm of the immune system responsible for parasite attrition and there is evidence indicating that parasite infection may prevent the development of some allergic conditions [4]. Given the obvious relationship between these disease states and the discovery of galectins in both parasitic organisms and tissues subject to allergic responses, it was decided to review the possible roles of galectins in both conditions.

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Galectins in parasite infections

Parasitology research, including the study of galectin involvement in parasite infection, requires an examination of the biology of both the parasite and the host. Helminth parasites possess their own complement of galectins most of which may function in the normal morphological development of a multicellular organism such as those found in the free living nematode worm, *Caenorhabditis elegans*, while others may be specifically adapted or evolved to facilitate parasite survival in a hostile host. On the other hand, host galectins are implicated in both establishing and combating parasite infections.

Galectins have been found in various life forms from invertebrates to vertebrates and even fungi, so it comes as no surprise that galectins have been isolated from a number of helminth parasites including *Onchocerca volvulus* [5], *Teladorsagia circumcincta* [6], *Haemonchus contortus* and *Trichostrongylus colubriformis* [7]. Comparison of the protein sequences of the galectins isolated from *T. circumcincta*, *H. contortus* and *T. colubriformis* showed little variation in their amino acid

sequences [7]. Moreover, western blotting experiments with antibodies raised to *T. colubriformis* galectin detected presumably similar galectins in a range of parasites from phylogenetically diverse families including *Taenia serialis* and *Fasciola hepatica*, as well as a number of additional nematode species [7]. These results indicate that parasite galectins are probably evolutionarily conserved and involved in a crucial yet similar function for each parasite, despite the differences in parasitic host, life cycles and environments.

As yet no function has been attributed to parasite/nematode galectins, although it has been speculated that they may perform similar functions as their vertebrate relatives [8,9]. However, recent analysis of the evolution of lectin-like proteins has suggested that galectins have evolved via independent radiation in the vertebrate and invertebrate lineages and thus may perform distinct functions [10]. It is possible that parasite galectins are involved in host-parasite interactions. For example, a galectin from *O. volvulus* was recognised by sera from the majority of filaria-infected patients and was able to bind IgE, however, it is unclear what role it plays in the pathophysiology of this infection [5].

The development of an immune response to a parasite requires that the cells of the immune system recognise the invader. Often the first point of recognition is the parasite's surface; these are generally highly glycosylated and thus potential galectin binding sites. In this respect, there are examples of host galectins binding directly to glycoconjugates on the surface of microorganisms, leading to both positive and negative regulation of host immunity. A macrophage membrane bound protein homologous to galectin-3 binds to β1,2-linked oligomannosides on the cell wall of *Candida albicans***,** potentially triggering a macrophage response which may promote the intracellular accommodation of this parasite and/or induce the release of cytokines to prime a protective immune response [11]. Similarly, galectin-9 appears to specifically recognise the major surface lipophosphoglycans of the protozoal parasite, *Leishmania major* and promote parasite binding to macrophages, thus potentially assisting parasite cell invasion and infection [12]. Galectin-3 also recognises *L. major* surface lipophosphoglycans [13]. This association leads to the cleavage of galectin-3, resulting in a truncated form of galectin-3 incapable of oligomerisation, thereby rendering it functionally inactive; an outcome that is likely to be beneficial to the parasite. This process is very similar to the cleavage of surface bound antibodies by the blood fluke, *Schistosoma mansoni* which inactivates antibody-mediated defence mechanisms [14]. The protozoal parasite, *Trypanosoma cruzi*, also seems to utilise galectin-3 to adhere to the extracellular matrix via surface glycoprotein recognition [15]. It does appear therefore, that parasites can manipulate the recognition of surface glycoconjugates by galectins to facilitate their survival.

Although not involved in specific recognition of surface molecules, galectin-1 may be another host galectin involved in host/parasite interactions, specifically during *T. cruzi* infection. Chagas' disease, caused by *T. cruzi*, is accompanied by the upregulation of galectin-1 expression and the development of anti-galectin-1 IgE [16]. Of particular interest, galectin-1 has recently been shown to be a significant modulator of the immune response as it is able to downregulate IL-2 and IFN-γ expression by T cells while maintaining IL-10 production, thereby skewing the immune response to a T2- phenotype [17,18]. IFN-γ is implicated in *T. cruzi* replication, suggesting that galectin-1 production favours chronic establishment of the parasite. While low concentrations of galectin-1 can lead to an increase in parasite replication and a down-regulation of mediators for parasite killing in infected macrophages, high concentrations can trigger macrophage apoptosis and inhibit parasite replication [19].

While searching for molecules that were specifically upregulated in nematode-infected tissues, another galectin-like protein was recently identified in sheep [20], tentatively named galectin-11 although carbohydrate binding activity has not yet been demonstrated. The detection of high levels of galectin-11 mRNA in helminth infected, but not control, gastrointestinal tissues suggests that this galectin is involved in the immune/inflammatory response to these parasites. In particular, galectin-11 expression was only induced in tissues infected with the larval and not the adult stages of the parasite, suggesting its induction is specifically associated with the eosinophil-rich inflammatory response typical for larval infections [3,21]. Localisation studies indicated that galectin-11 was secreted in large quantities (μg/ml range) from epithelial cells into the lumen of infected sheep, where it may interact with mucins or other glycoconjugates within the mucus and form part of an anti-parasite effector mechanism. The gastrointestinal mucus of nematode-infected sheep and mice has been shown to contain as yet unidentified immune mediators that affect motility of helminth larvae [22,23]. Galectin-11 may function in an analogous manner to galectin-1, which has been shown to bind mucins and glycocalyces of the gastrointestinal tract, and through cross-linking may form a permanent protective barrier against foreign organisms [24]. However, the inducible aspect of galectin-11 compared to galectin-1 in the gastrointestinal tract suggests that it has a more specific role for protection against helminth pathogens. Further investigation is required to establish the precise role of galectin-11 in gastrointestinal inflammation and protection of the gastrointestinal tract from infection. It is of interest, that galectin-11 is induced during primary infection of naïve sheep and, at an accelerated rate, during challenge infection of primed sheep suggesting it may be involved in both the innate and adaptive immune response to gastrointestinal parasite infection [20].

The immune response of mammals to multicellular parasite infection, like that of an allergic response, is characterised by the recruitment of eosinophils from the blood to affected tissues sites [21,25]. Eosinophils are capable of releasing a battery of potent cytotoxic and proinflammatory agents including peptide, cytokine and lipid mediators that are thought to play an important role in host defence against parasite infections, but

also contribute to tissue dysfunction and damage in a number of allergic diseases including asthma [26]. There are a number of galectins that are associated with eosinophils, either expressed by them, galectin-3, -10 and -14 [27–29], or involved in eosinophil recruitment, galectin-9 [30]. For example, galectin-3 is expressed on the surface of eosinophils and is thought to modulate eosinophil function through its ability to bind IgE. Inhibition of galectin-3 by anti-galectin-3 mAb produces a dose-dependent reduction in human eosinophil-mediated cytotoxicity to parasite targets *in vitro*, suggesting that galectin-3 is involved in eosinophil effector functions to combat parasitic infections [27].

In contrast to the broad expression of most other galectins, galectins 10 and 14 are unique in their restricted expression by eosinophils, and possibly basophils [29,31,32]. Galectin-10, otherwise known as the Charcot-Leyden crystal, was initially thought to be a lysophospholipase, however recent studies have discounted this theory and, with a weak affinity for β-galactoside sugars, have confirmed its classification as a true galectin [28,33,34]. Despite the similarity in their expression profiles, human galectin-10 and ovine galectin-14 do not appear to be homologues showing only 25% amino acid identity [20]. Instead, galectin-14 is most similar to the N-terminal part of galectin-9, with 57% identity to human galectin-9, making the issue of identifying orthologues unresolved. Although the function of these two galectins is unknown, the fact that they are found abundantly at sites of parasitic infection indicates that they may play an important role in eosinophil-mediated parasite attrition either directly or indirectly [29,35].

Galectins in allergic inflammation

The mechanisms of allergic inflammation and pathology have been studied extensively [2,36]. Allergens can cause degranulation of tissue mast cells by cross-linking surface receptors, either directly, or through binding to preformed IgE captured by mast cells of sensitised individuals. The mast cell mediators released exert a range of biological activities including vasodilation, increased vascular permeability, local proteolysis and the upregulation of adhesion molecules on vascular endothelial cells. The immediate allergic reaction caused by mast cell degranulation is followed by a more sustained inflammation characterised by the recruitment of other effector cells including eosinophils, basophils and T_H2 lymphocytes. This late phase response is an important cause of more serious long-term illness and can become converted into chronic inflammation if the allergen persists [36].

The high affinity IgE receptor (FcεRI) on mast cells is a glycoprotein, which is recognised by galectin-3 leading to mast cell activation [37]. Galectin-3 also recognises IgE, the most highly glycosylated of the immunoglobulin molecules [38,39]. This property of galectin-3 would enable it to cross-link FcεRI receptors in the presence and absence of IgE and allergen (reviewed by Liu [40]), activating mast cells to release preformed mediators and thus amplifying an allergic response. The notion that galectin-3 acts as an amplifier of allergic responses is supported by the finding that the level of surface galectin-3 increases when mast cells are activated by IgE immune complexes [41].

Galectins can also be involved in the late phase of an allergic reaction through the recruitment and activation of effector cells. Ecalectin/galectin-9 in particular has been identified as a potent eosinophil-specific chemoattractant and activating factor produced by antigen stimulated T-cells [30,42]. It differs structurally from other known eosinophil chemoattractants, IL-5 and eotaxin, and does not appear to use the same receptors. Galectin-9 induces eosinophil aggregation and superoxide release, both markers of eosinophil activation, but curiously does not induce degranulation. Galectin-9 is also able to promote eosinophil survival directly [42].

During recruitment, effector cells undergo a process of extravasation to pass from blood vessels, through the extracellular matrix into the tissues. Galectins 1, 3 and 8 are all known to bind to extracellular matrix proteins [43–48] suggesting that they may be involved in cell-matrix interactions, and regulation of immune cell passage into the tissues. Galectins 1 and 3 both appear to inhibit and promote adhesion to extracellular matrix proteins depending on the cell type and galectin concentration (reviewed by Hughes [49]). Galectin-8 can not only inhibit cell adhesion but, when immobilised onto a matrix, can itself act as a matrix protein equipotent to fibronectin, promoting cell adhesion, spreading, and triggering of integrin-mediated signalling cascades [48]. Recent research suggests that galectin-3 is specifically involved in the extravasation of neutrophils to the lungs during Streptococcal pneumonia, through direct cellular cross-linking in a manner independent of β_2 integrins [50]. This is in agreement with the findings that mice lacking galectin-3 show lower levels of granulocytes, lymphocytes and monocyte/macrophages in the peritoneal cavity following peritoneal thioglycollate stimulation [51,52]. While it is still unclear if this reduction in inflammatory cell numbers reflects an alteration in cell recruitment and/or cell death, the results support a role for galectin-3 in the recruitment and retention of inflammatory cells. It is yet to be determined if galectins also play a role in the accumulation and maintenance of inflammatory cells during allergic inflammation. Galectin-14 has been found at high concentrations (μg/ml range) in cell-free gastrointestinal mucus and lung fluid of parasite and allergen sensitised sheep, suggesting that it may be involved in inflammatory cell trafficking across epithelial surfaces [29]. Moreover, preliminary results with recombinant galectin-14 indicate that it can bind to laminin *in vitro* (AR Young, unpublished data), suggesting a possible role in the recruitment of eosinophils to sites of inflammation in a manner analogous to that of galectin-3 mediated neutrophil extravasation.

Once recruited from the blood to sites of inflammation, leukocytes are stimulated to release additional proinflammatory mediators and cytokines, which perpetuate the allergic response

[2]. Cells typically associated with allergic inflammation, basophils and eosinophils, both express the high affinity FcεRI [53,54]. Although the functional significance of the FcεRI in eosinophils is unclear [55], both cell types theoretically have the potential to be activated by both IgE and/or galectin-3 in a manner analogous to that of mast cell activation [37]. Eosinophils also express galectin-3 on their surface and the addition of anti-galectin-3 antibody produces a dose-dependent inhibition of IgE-dependent effector function [27]. It is interesting therefore to draw an analogy between the IgE-dependent activation of eosinophils and that of another granulocyte, the neutrophil. Neutrophils also express galectin-3 on their surface, and blocking of this molecule with antibodies can inhibit IgE-dependent activation, as measured by respiratory burst activity [56]. However, galectin-3 has also been found to directly stimulate superoxide production by neutrophils, probably by cross-linking surface glycoprotein receptors [57]. Galectin-3 is expressed by a number of inflammatory cell types, including mast cells, monocytes, macrophages, neutrophils and eosinophils [27,41,56,58], and as such is likely to be available at sites of allergic inflammation to modulate effector cell function in an autocrine or paracrine fashion. In addition, other galectins such as galectin-10 and 14 [29,59] are only found at high concentrations at sites of allergic inflammation, possibly indicating a role in the modulation of effector cell function analogous to that of galectin-3, but with a more specific target considering their restricted expression in eosinophils and basophils only.

Contrary to the evidence of galectin-3 as an activator of effector cells, it was recently discovered that galectin-3 could down-regulate IL-5 expression in a number of different cell types, including eosinophils [60]. IL-5 is important in the development, differentiation, activation, survival and trafficking of eosinophils [61], suggesting that galectin-3 regulation of IL-5 levels may form part of a feedback mechanism to regulate the number of eosinophils at sites of inflammation.

Conclusion

Galectins are becoming increasingly identified as mediators of the immune response, and, more recently, in the allergic inflammatory response induced by helminth parasites and allergens. With the increasing number of different galectins identified and their inherent functional diversity, it seems likely that they may be involved at different levels of both the innate and adaptive immune response. The involvement of C-type lectins such as mannose-binding lectin (MBL) in the innate recognition of pathogen molecules has been well established [36,62], and binding of galectin-3 and -9 to *Leishmania* lipophosphoglycans may indicate a similar pattern recognition receptor (PRR) function for some galectins. In this respect, it is interesting to note that helminth parasites at different developmental stages carry glycoconjugates with novel combinations of glycans, containing β-galactosides [63,64]. It is possible that the presence of different parasitic stages is communicated to the host's innate immune system through galectin recognition of their unique carbohydrate epitopes, although this remains to be demonstrated.

The ability of some galectins, such as galectin-1 and galectin-3 to modulate the differential expression of cytokine genes in leukocytes may also extend to other galectins and signify an important role for galectins in directing the nature of the adaptive immune response, in particular towards a T2-type allergic response. The switching of T cell phenotypes by galectins can have important implications for disease treatment strategies as illustrated by the ability of galectin-1 to alleviate autoimmune encephalomyelitis and arthritis in experimental rodent models [65,66]. It also seems likely that galectins may play an important role in activation and recruitment of inflammatory cells, with the possibility of targeting specific effector cell types by different galectins.

Most of the proposed functions for galectins have been extrapolated from *in vitro* culture studies. There is an urgent need to examine the functional activity of galectins within the microenvironment in which they are produced or secreted and to test their role in *in vivo* disease models. In particular, the specific activity of galectins on eosinophils, basophils and mast cells and their ability to reduce the severity of T1-type pathologies through switching to a T2-type immune response, suggests that they may be pro-active in instigating the allergic-type response induced by helminth parasite infections and allergen challenge. Functional *in vivo* studies in parasite and allergy models would therefore be useful in clarifying the role of galectins in allergic inflammation.

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