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Review Article

Galectins as immunoregulators during infectious processes: from microbial invasion to the resolution of the disease

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SUMMARY

Recent evidence has implicated galectins, a family of evolutionarily conserved carbohydrate-binding proteins, as regulators of immune cell homeostasis and host–pathogen interactions. Galectins operate at different levels of innate and adaptive immune responses, by modulating cell survival and cell activation or by influencing the Th1/Th2 cytokine balance. Furthermore, galectins may contribute to host–pathogen recognition and may serve as receptors for specific interactions of pathogens with their insect vectors. Here we will explore the influence of galectins in immunological processes relevant to microbial infection and will summarize exciting recent work related to the specific interactions between galectins and their glycoconjugate ligands as critical determinants of pathogen recognition. Understanding the role of galectin–sugar interactions during the course of microbial infections might contribute to defining novel targets for disease prevention and immune intervention.

Keywords *apoptosis, cytokines, galectins, host–pathogen interactions, infection*

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INTRODUCTION

Biochemistry and classification of galectins

Galectins, a growing family of evolutionarily conserved carbohydrate-binding proteins, have recently attracted the attention of immunologists as novel regulators of immune cell homeostasis and host–pathogen interactions (1,2). Members of the galectin family are defined by a conserved carbohydrate-recognition domain (CRD) with a canonical amino acid sequence and affinity for β-galactosides (3,4). To date, 15 mammalian galectins have been identified, which can be subdivided into those that have one CRD and those that have two CRDs in tandem. In addition, galectin-3, a one-CRD galectin, is unique in that it contains unusual tandem repeats of short amino-acid stretches fused onto the CRD (4,5) (Figure 1). In addition, analysis of genome data bases has led to the identification of additional candidate galectin genes in the genomes of invertebrates (worms and insects) and protists (sponges and fungi). In addition, galectin genes are also present in the genomes of important model organisms including zebrafish, *Drosophila*, *Anopheles gambiae* and even in protozoan parasites and viruses, suggesting that these sugar-binding proteins are indeed highly conserved throughout evolution (3).

Many galectins are either bivalent or multivalent with regards to their carbohydrate-binding activities – some one-CRD galectins exist as dimers; two-CRD galectins have two carbohydrate-binding sites; and galectin-3 forms oligomers when it binds to multivalent carbohydrates (5) (Figure 1). In this way, galectins can form ordered arrays of complexes when they bind to multivalent glycoconjugates, much like the lattices formed by antibodies and multivalent antigens (6). Some galectins are distributed in a wide variety

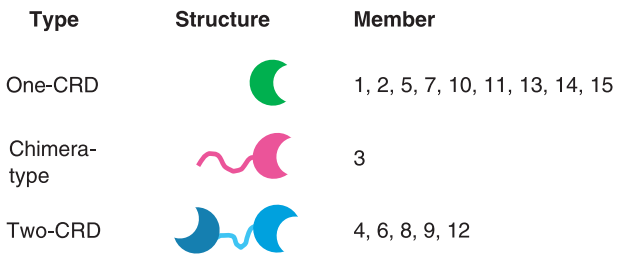

Figure 1 Schematic representation of the structure of different members of the galectin family. Galectins are a family of animal lectins characterized by conserved carbohydrate-recognition domains (CRDs) consisting of about 130 amino acids that are responsible for carbohydrate binding. So far, 15 mammalian galectins have been identified. They can be subdivided into three groups: those containing one CRD (galectin-1, 2, 5, 7, 10, 11, 13, 14 and 15); those containing two distinct CRDs in tandem, connected by a linker of up to 70 amino acids (galectin-4, 6, 8, 9 and 12); and galectin-3 which consists of unusual tandem repeats of proline- and glycine-rich short stretches fused onto the CRD.

of tissues, whereas others have a more restricted localization. The expression of galectins is modulated during the differentiation and activation of immune cells and changes under different physiological or pathological conditions.

Galectins are present both inside and outside cells, and function both intracellularly and extracellularly. Although galectins have features of cytosolic proteins, they are secreted by non-classical (non-ER-Golgi) pathways (4). Extracellularly, galectins can bind to cell-surface glycoconjugates that contain suitable galactose-containing oligosaccharides. As galectins can bind either bivalently or multivalently, they can crosslink cell-surface glycoconjugates, which, like many other receptor–ligand systems, can trigger a cascade of transmembrane signalling events. Through this mechanism, galectins modulate processes that include apoptosis, cytokine secretion and host–pathogen interactions (2). Intracellularly, galectins are engaged in processes that are essential for basic cellular functions such as pre-mRNA splicing, regulation of cell growth and cell cycle progression (5,7).

Galectins: friends or foes during infection?

During an infectious process, a battle for survival takes place between the host and the microorganism. As a consequence of these complex interactions, the infection can be resolved, the pathogen can be controlled but not eliminated, leading to chronic persistence in the host, or the infection can proceed unimpeded and kill the host.

By recognizing specific glycoconjugates, galectins may contribute to almost any step involved in host–pathogen interactions and may regulate the magnitude and quality of the immune response following infection. Galectins are widely expressed by a variety of cells in central and peripheral immune compartments, including thymic epithelial cells (8), antigen-primed T cells (9,10), macrophages (11–13), eosinophils (14), and activated B cells (15,16). Interestingly, expression of different members of the galectin family is up-regulated during immune cell activation (11,15,17) or following infection of these cells with different pathogenic bacteria, viruses, fungi and parasites (12,15). For example, galectin-1 and galectin-3 are up-regulated in immune cells following infection with *Trypanosoma cruzi*, *Streptococcus pneumoniae*, Human Immunodeficiency Virus-1 (HIV-1) and Human T Lymphotropic Virus-1 (HTLV-1) (12,13,15–20).

Further work is now warranted to determine whether galectins can negatively or positively affect microbial invasion and whether they are involved in the resolution of infection. Here we will discuss recent advances on the role of galectins in immunoregulation and host–pathogen interactions (Figure 2).

GALECTINS AND IMMUNOREGULATION

Galectins and the modulation of cell survival: implications for host–pathogen interactions

Apoptosis is a genetically controlled, morphologically and biochemically distinct form of programmed cell death that occurs during immune cell development and maturation, effector cytotoxic T cell responses, peripheral tolerance and immune cell homeostasis (21). Regulation of host cell apoptosis has been shown to be a critical determinant during microbial invasion and resolution of infection (22, 23). Whilst some pathogens actively inhibit apoptosis of their host cells in order to maintain a latent infection, others promote apoptosis of different immune cell types (23–25). Intracellular protozoa may express anti-apoptotic molecules to block apoptosis of the infected host cell, allowing completion of the life cycle. Then, at a critical phase of the cell cycle, the pathogen may begin to express a set of pro-apoptotic molecules, which would induce host cell apoptosis in order to spread infection (22). Hence, the balance between anti-apoptotic and pro-apoptotic signals might be developmentally regulated and exploited by microbes for their benefit. On the other side, the host immune response may induce apoptosis of infected target cells in order to damage intracellular pathogens (21,22).

Galectins have recently emerged as novel regulators of the inflammatory response and immune cell homeostasis (1) (Table 1). In this context, the most extensively studied function of galectins is the regulation of apoptosis. It has been reported that galectin-1 induces apoptosis of activated T cells and immature cortical thymocytes (11,26–29). The

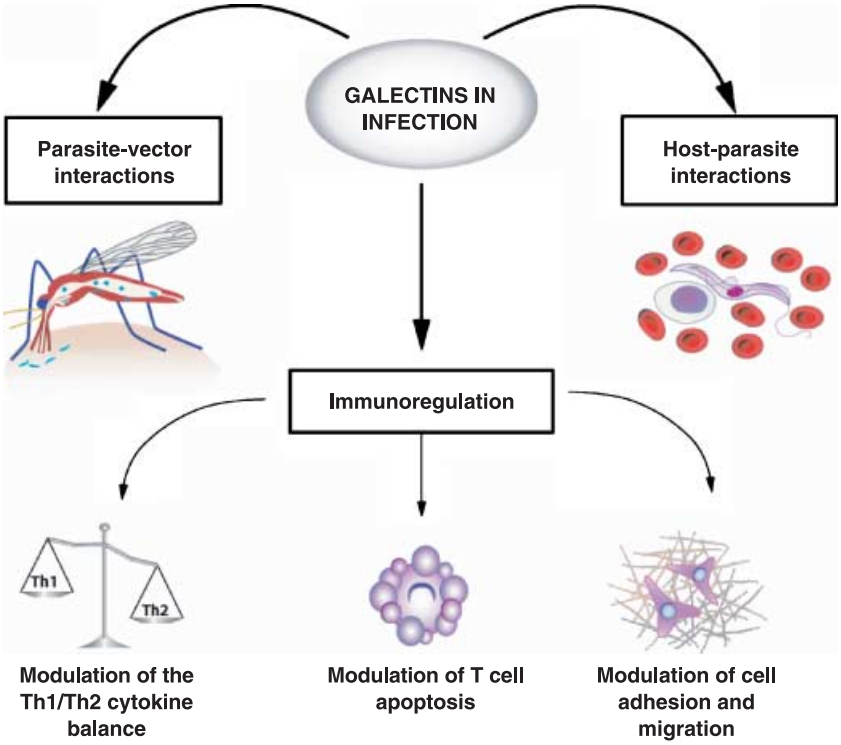

Figure 2 Role of galectins in the pathogenesis and resolution of infectious diseases. Galectins play major roles in the regulation of innate and adaptive immune responses (e.g. immune cell survival, Th1/Th2 cytokine production, immune cell differentiation and cell–extracellular matrix interactions). Recent findings indicate that galectins may also play critical roles in the interactions between pathogens and mammalian hosts or insect vectors, suggesting their contribution to microbial invasion.

signal transduction events that lead to galectin-1-induced apoptosis include the induction of specific transcription factors (i.e. AP-1), the modulation of Bcl-2 protein production, activation of caspases, modulation of the ceramide pathway and release of cytochrome c (30,31). However, a recent study shows that apoptosis induced by galectin-1 in a T-cell line is not dependent on the activation of caspase-3 or on cytochrome c release (32). Furthermore, recent evidence indicates that galectin-1 can induce the exposure of phosphatidylserine on the plasma membrane of T cell lines and activated neutrophils but that this effect does not result in apoptosis (33). Therefore, it seems that galectin-1 might trigger different death pathways or different apoptosis end points in different cell types.

It has been shown that galectin-1 can bind to unique subsets of cell-surface glycoprotein receptors, including CD45, CD43 and CD7 on the surface of thymocytes, activated T lymphocytes and T-cell lines, inducing segregation of these receptors into membrane microdomains (34). Interestingly, the susceptibility to galectin-1-induced apoptosis can be controlled by the addition and/or modification of *N*-acetyllactosamine sequences displayed on either *N*- or *O*-glycans decorating these glycoreceptors. While the core 2 β-1,6-*N*-acetylglucosaminyltransferases (C2GnTs) allow elongation of *O*-linked polylactosamine chains which participate in galectin-1 binding to T cells and the initiation of T cell death (35), other glycosyltransferases such as the α2,6-sialyltransferase I (ST6Gal I) (36) may act to reduce galectin-1 binding and modulate galectin-1-induced cell death. Interestingly, recent striking findings indicate that altered glycosylation of T cells during HIV-1 infection increases their susceptibility to galectin-1-induced cell death (37), suggesting that this apoptotic pathway may contribute to HIV-1-induced immunosuppression.

The pathophysiological relevance of galectin-1-induced cell death *in vivo* has been demonstrated in experimental models of chronic inflammation (38–41). Administration of galectin-1 *in vivo* suppresses Th1-dependent immune responses by increasing T-cell susceptibility to activation-induced cell death (AICD) and skewing the balance of the immune response towards a Th2-type profile (38,39). Furthermore, we have recently shown that expression of galectin-1 confers immune privilege to tumour cells by modulating survival and polarization of $CD4^+$ and $CD8^+$ T cells (42).

A major concern regarding the pro-apoptotic activity of galectin-1 is that this effect has, in most cases, been demonstrated only at relatively high galectin concentrations (micromolar range) and it is uncertain whether such high levels of soluble protein can be produced *in vivo*. Interestingly, however, recent evidence indicates that the amount of galectin-1 secreted by different cell types is sufficient to kill T cells when galectin-1 is presented in the context of

Table 1 Immunoregulatory effects of galectins and their influence in infectious processes

	Biochemical structure	Immunoregulatory effects	Influence in infectious processes
Galectin-1	One-CRD galectin (monomeric or dimeric)	Induces apoptosis of immature thymocytes and activated T cells Modulates cytokine production (Th2 bias) Inhibits acute inflammatory processes Inhibits neutrophil extravasation and mast cell degranulation Suppresses chronic inflammation and autoimmunity	Up-regulated expression during infections with *T. cruzi* and *H. pylori* Altered glycosylation of T cells during HIV-1 infection increases the susceptibility of T cells to galectin-1-induced cell death Promotes HIV-1 infectivity
Galectin-2	One-CRD galectin	Increases lymphotoxin-α release from macrophages Induces T-cell apoptosis	NS
Galectin-3	Chimera type	Promotes macrophage phagocytosis Induces monocyte chemotaxis Mediates cell–matrix interactions Modulates cytokine production Prevents T-cell apoptosis (intracellularly) Promotes T-cell and neutrophil apoptosis (extracellularly) Modulates neutrophil degranulation and survival Promotes NADPH oxidase activation Restricts TCR-mediated signal transduction	Up-regulated during infections with *T. cruzi*, HTLV-I, HIV-I, *H. pylori* and *S. pneumoniae* Interacts with mycobacterial phosphatidylinositol mannosides Interacts with LPS of Gram (–) bacteria Interacts with oligomannosides from *C. albicans* Interacts with *T. cruzi* trypomastigotes Binds lipophosphoglycans present in *L. major* Inhibition of galectin-3 favours plasma cell differentiation and increases the levels of parasite specific antibodies, resulting in parasite clearance and disease amelioration in an experimental model of *T. cruzi* infection Mediates the adhesion of neutrophils to the endothelium during streptococcal pneumonia
Galectin-4	Two-CRD galectin	Increases $CD4^+$ T cell activation	NS
Galectin-8	Two CRD galectin	Modulates neutrophil functions associated with microbial invasion	NS
Galectin-9	Two-CRD galectin	Acts as a potent eosinophil-specific chemoattractant Increases thymocytes and T-cell apoptosis	Promotes the interaction between *L. major* and macrophages

No immunological functions have been described for galectins-5, -6, -7, -10, -11, -12, -13, -14 and -15. NS Not studied.

extracellular matrix (ECM) glycoproteins (29). Furthermore, the secretion of galectin-1 from activated but not resting T cells (9,17) suggests a potential autocrine suicide mechanism to achieve homeostasis following the completion of an immune response. Furthermore, other galectins including galectin-2 (43), galectin-3 (44) and galectin-9 (45) have been shown to promote T-cell apoptosis, suggesting that the immunoregulatory properties of galectin-1 may also be extended to other members of the galectin family.

The second approach for studying the role of galectins in cell apoptosis was the transfection with a cDNA encoding an individual galectin. This approach was most successful for galectin-3, in this case clearly demonstrating its anti-apoptotic activity in a range of cell types exposed to diverse apoptotic stimuli (46,47), findings which were confirmed by inhibition of galectin-3 by an oligonucleotide antisense which specifically inhibited proliferation of antigen-stimulated T cells (10). Furthermore, peritoneal macrophages from galectin-3-deficient mice displayed higher levels of apoptosis, when compared to cells from wild-type mice, suggesting that this sugar-binding protein also protects macrophages from cell death (48). An examination of the mechanisms responsible for this effect revealed that galectin-3 might act intracellularly by preventing alterations of the mitochondrial membrane and formation of reactive oxygen species (49). Moreover, it has been reported that galectin-3 phosphorylation is important for its anti-apoptotic activity (50). On the other hand, cells overexpressing galectin-7 are more likely than control cells to undergo apoptosis induced by a wide variety of apoptotic stimuli (51), and galectin-12 promotes apoptosis when it is overexpressed in a fibroblast cell line (52).

This complex scenario, with many members of the galectin family modulating immune cell fate, raises important questions which remain to be addressed. Do members of the galectin family contribute to immunoregulation and immune cell apoptosis during the course of intracellular or extracellular infections? Do pathogens modulate the galectin-dependent death machinery to survive inside their host cells? Do pathogens synthesize galectin-like molecules or modulate the expression of different host galectins to control immune cell apoptosis and thwart the development of specific host defences? Future work is warranted to address these important questions.

Galectins and the regulation of immune cell activation and differentiation

Immune cell activation and differentiation are key processes which determine the successful resolution of an inflammatory response following an antigenic challenge. In this context, 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 (53). In contrast, Demetriou and colleagues (54) reported that galectin-3 might play a role in restricting T-cell receptor (TCR) complex-initiated signal transduction. The authors hypothesize that galectin-3 forms multivalent complexes with *N*-glycans on the TCR, thereby restraining the lateral mobility of TCR complexes (54). On the other hand, galectin-1 has been reported to antagonize T-cell activation by inducing partial TCR-ζ chain phosphorylation (55), while galectin-4 has been shown to contribute to activation of $CD4^+$ T cells (56).

Regarding the B-cell compartment, we have recently demonstrated that galectin-3 is a critical mediator of B-cell differentiation and survival (16). Blockade of intracellular galectin-3 using an antisense strategy abrogated IL-4-induced survival of activated B cells and favoured differentiation towards a plasma cell pathway. Moreover, B cells with restrained galectin-3 expression failed to down-regulate the Blimp-1 transcription factor following IL-4 stimulation. *In vivo*, targeted inhibition of galectin-3 favoured plasma cell differentiation and increased the levels of specific immunoglobulin production, resulting in parasite clearance and disease amelioration in an experimental model of *T. cruzi* infection (16).

In addition to the influence of galectins in the T- and B-cell compartments, previous studies also reported the regulated expression and potential role of galectins in the differentiation of myeloid cells (57). Taken together, these findings allow us to speculate that the regulated expression of galectins during the course of a microbial infection might be relevant in the activation, differentiation and survival of immune cells, i.e. in critical immunological events implicated in the resolution of infectious processes. This hypothesis remains to be tested in experimental models of infection.

Galectins in the control of the Th1/Th2 cytokine balance

The Th1/Th2 cytokine balance is crucial for determining the outcome of many infections. Galectins may modulate cytokine secretion in favour of either the pathogen or the host. Galectin-1 has been shown to block secretion of pro-inflammatory cytokines, including IL-2, interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α) (55,58). In addition, *in vivo* studies in experimental models of chronic inflammation revealed the ability of galectin-1 to skew the balance towards a Th2-type cytokine response, with decreased levels of IFN-γ and increased secretion of IL-5 by pathogenic T cells (38–41). In the context of infection, we have demonstrated in an experimental model of *T. cruzi* infection that very low concentrations of galectin-1 (nanomolar range) are sufficient to down-regulate the production of IL-12 (a critical cytokine required for parasite killing) from infected macrophages without affecting the secretion of type-2 cytokines. Interestingly,

we found a biphasic modulation of parasite replication and cell viability when macrophages isolated from *T. cruzi*-infected mice were exposed to increasing concentrations of galectin-1 (12). While low concentrations of this protein promoted parasite replication by down-regulating critical mediators for parasite killing (IL-12 and nitric oxide), higher doses of galectin-1 were able to commit infected cells to apoptosis, thereby inhibiting parasite replication (12).

Consistent with a role for galectin-1 in immunosuppression, van der Leij and colleagues (59) recently demonstrated a marked increase in IL-10 mRNA and protein levels in non-activated and activated $CD4^+$ and $CD8^+$ T-cells, following treatment with a high concentration of recombinant galectin-1. Since IL-10 is known to suppress Th1-type immune responses, up-regulation of IL-10 may thus contribute to the immunomodulatory activity of galectin-1.

On the other hand, galectin-3 behaves in most cases as a 'pro-inflammatory cytokine', as has been demonstrated by the attenuated inflammatory response in galectin-3 knockout mice (48). However, this lectin also suppresses type-2-mediated allergic inflammation by blocking IL-5 synthesis in human eosinophils and antigen-specific T-cell lines (60). These data suggest, that under distinct physiological or pathological conditions, different members of the galectin family may provide inhibitory or stimulatory signals to modulate immune cell homeostasis and regulate inflammation following an antigenic challenge. Although, the mechanisms of galectin-mediated modulation of cytokine production are still obscure, we may hypothesize that different galectin family members might trigger different signalling cascades to modulate the expression of different transcription factors involved the regulation of cytokine synthesis. Since galectin-1 and galectin-3 have been shown to differentially modulate both the Th1/Th2 cytokine balance and cell survival, intracellular and extracellular infections represent excellent model systems in which to try to correlate galectin activity with the outcome of infection and to dissect the contribution of each galectin to host–parasite interactions.

Galectins and the regulation of innate immune responses

In addition to their effects on T cell activation, galectins have been shown to influence the development of effective innate immune responses (61). We have demonstrated that galectin-1 suppresses the acute inflammatory response and inhibits neutrophil extravasation (62). Furthermore, this lectin suppresses arachidonic acid release and nitric oxide production from activated macrophages (62,63). In addition, recent findings indicate that galectin-1 can inhibit neutrophil chemotaxis and transendothelial migration (64).

In contrast to the anti-inflammatory effects of galectin-1, studies of induced peritonitis in galectin-3-deficient mice provided significant support for the pro-inflammatory role of this lectin (48,65). After intraperitoneal injection of thioglycolate, galectin-3-deficient mice had significantly reduced numbers of recoverable granulocytes compared to wild-type animals (48,65). Interestingly, however, Karlsson and colleagues showed that both galectin-1 and galectin-3 can induce activation of the superoxide-producing NADPH-oxidase at similar levels in primed neutrophils (66,67).

Regarding the role of galectins in cell–cell and cell–ECM interactions, galectin-3 has been shown to promote neutrophil adhesion to laminin (68). Moreover, Sato and colleagues showed that galectin-3 is up-regulated in endothelial cells following *Streptococcus pneumoniae* infection and that this protein mediates neutrophil adhesion to endothelial cells *in vitro* (18). On the other hand, it has been reported that galectin-3 can act as a de-adhesion molecule under certain circumstances and in different microenvironments (69).

Recently, Liu and colleagues highlighted a critical role for galectin-3 in phagocytosis by macrophages (70). Compared with wild-type macrophages, galectin-3-deficient cells exhibited reduced phagocytic capacity (70). In addition, the same group showed that galectin-3 promotes chemotaxis of human monocytes through interaction with a G-protein coupled receptor (71) and we have recently shown that galectin-3 acts in concert with soluble fibrinogen to regulate neutrophil activation, survival and degranulation through modulation of alternative mitogen-activated protein kinases (MAPK) pathways (72). A summary of the immunoregulatory effects of galectins-1 and -3 is shown in Figures 3 and 4, respectively.

Although not studied as extensively as galectin-1 and galectin-3, other galectins also modulate innate immune response. For example, galectin-8 can modulate neutrophil functions related to microbial killing (73) and galectin-2 can regulate lymphotoxin-α secretion from macrophages (74). On the other hand, galectin-9 (also called ecalectin) has been identified as a potent eosinophil-specific chemoattractant (75), suggesting its potential role in the modulation of allergic reactions and worm infections.

ANTI-GALECTIN ANTIBODIES DURING INFECTION

Despite the fact that galectins are highly conserved throughout animal evolution, antigalectin-1 autoantibodies have been described in the acute and chronic stages of human Chagas' disease (76). Giordanengo and colleagues reported a marked increase in the level and frequency of antigalectin-1 IgE in sera from patients with acute infection (76) and antigalectin-1 IgG immunoreactivity correlated with the severity of cardiac damage in patients suffering from chronic Chagas' disease (76). These antibodies have also been

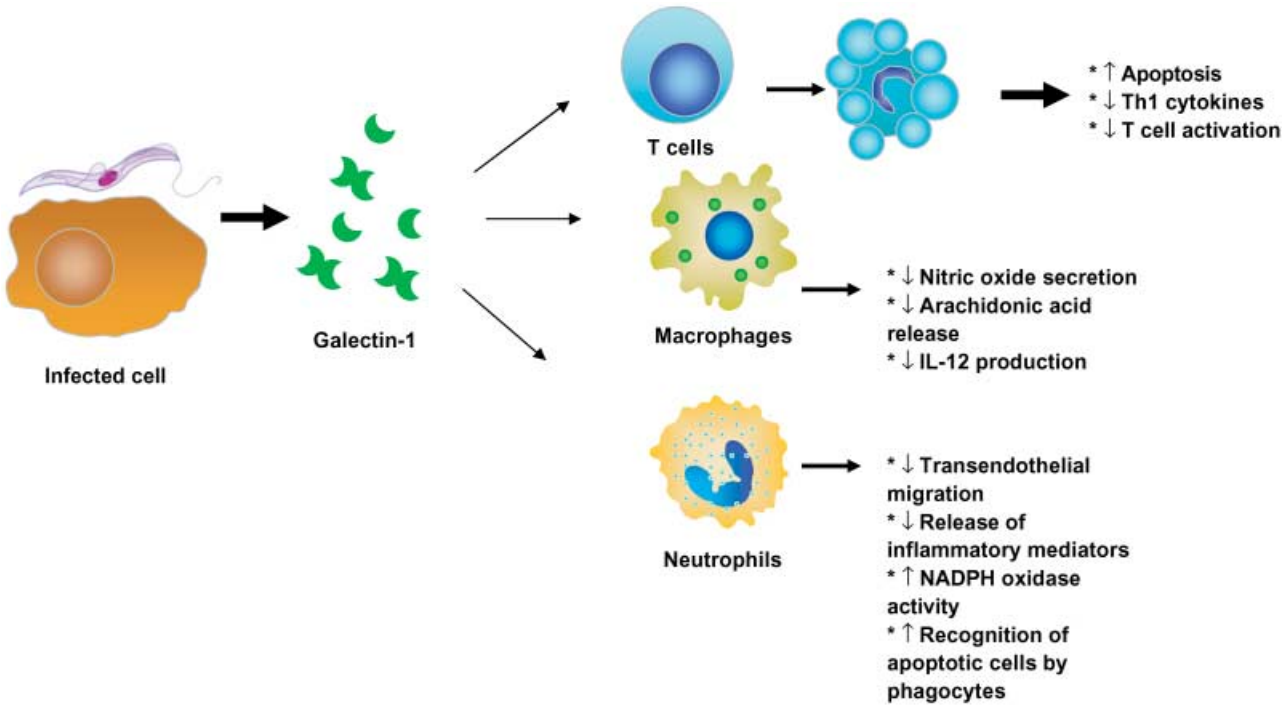

Figure 3 Influence of galectin-1 in the physiology of different immune cell types. Galectin-1 is up-regulated following infection with various infectious agents (details are provided in the text). This scheme illustrates the influence of galectin-1 secreted by infected cells in the physiology of T cells, macrophages and neutrophils. Other galectins also contribute to immunoregulation but less is known about their biological effects.

described in other clinical settings, in particular in autoimmune disorders (reviewed in 2). Whether these antibodies could influence the pathogenesis of the disease or whether they could be markers of the severity of infectious processes still remains to be elucidated.

GALECTINS IN HOST–PATHOGEN INTERACTIONS: THE SWEET ENCOUNTER

The multivalent properties of galectins make these proteins suited for cell adhesion functions, suggesting that they could also be engaged in host–pathogen interactions. In fact, β-galactoside-related carbohydrates (polygalactose epitopes) are commonly present in pathogen-associated glycoconjugates, leading to the suggestion that galactose-binding proteins may act as host receptors for bacteria, viruses, fungi and parasites and there are now several examples in the literature of apparent direct or indirect galectin-dependent specific host–pathogen interactions.

Bacteria and fungi

Immunoblot analysis revealed expression of galectin-3 by prostate epithelial cells invaded by gonococci (77), and galectin-1 and galectin-3 are up-regulated in gastric epithelial cells infected with *Helicobacter pylori*, suggesting that galectins might contribute to bacterial invasion (78). There is also evidence for a role for galectin-3 in mycobacterial infection; galectin-3 appears to bind to mycobacterial phosphatidylinositol mannosides (PIMs), accumulating at the cytosolic face of the phagosome membrane in phagosomes containing live mycobacteria, demonstrating a novel interaction between host carbohydrate-binding proteins and mycobacterial glycolipids (79). Galectin-3 has also the ability to bind to gram-negative bacteria through recognition of different bacterial lipopolysaccharides (LPS) (80). For example, the carbohydrate-binding site in the C-terminal domain of galectin-3 interacts specifically with galactose-containing LPS from the bacterium *Klebsiella pneumoniae*, whilst the *N*-terminal domain of galectin-3 binds LPS from *Salmonella minnesota R7* (80). Galectin-3 can also interact with LPS from *Pseudomona aeruginosa* (81). The interaction of galectin-3 with LPS might allow the binding of pathogens to epithelial or immune cells.

In yeast, β-1,2-linked oligomannosides (associated with mannan and a phospholipomannan) are present at the *Candida albicans* cell wall surface (82) and interact with galectin-3, which is expressed in a wide variety of cells with which *C. albicans* interacts as a saprophyte or parasite.

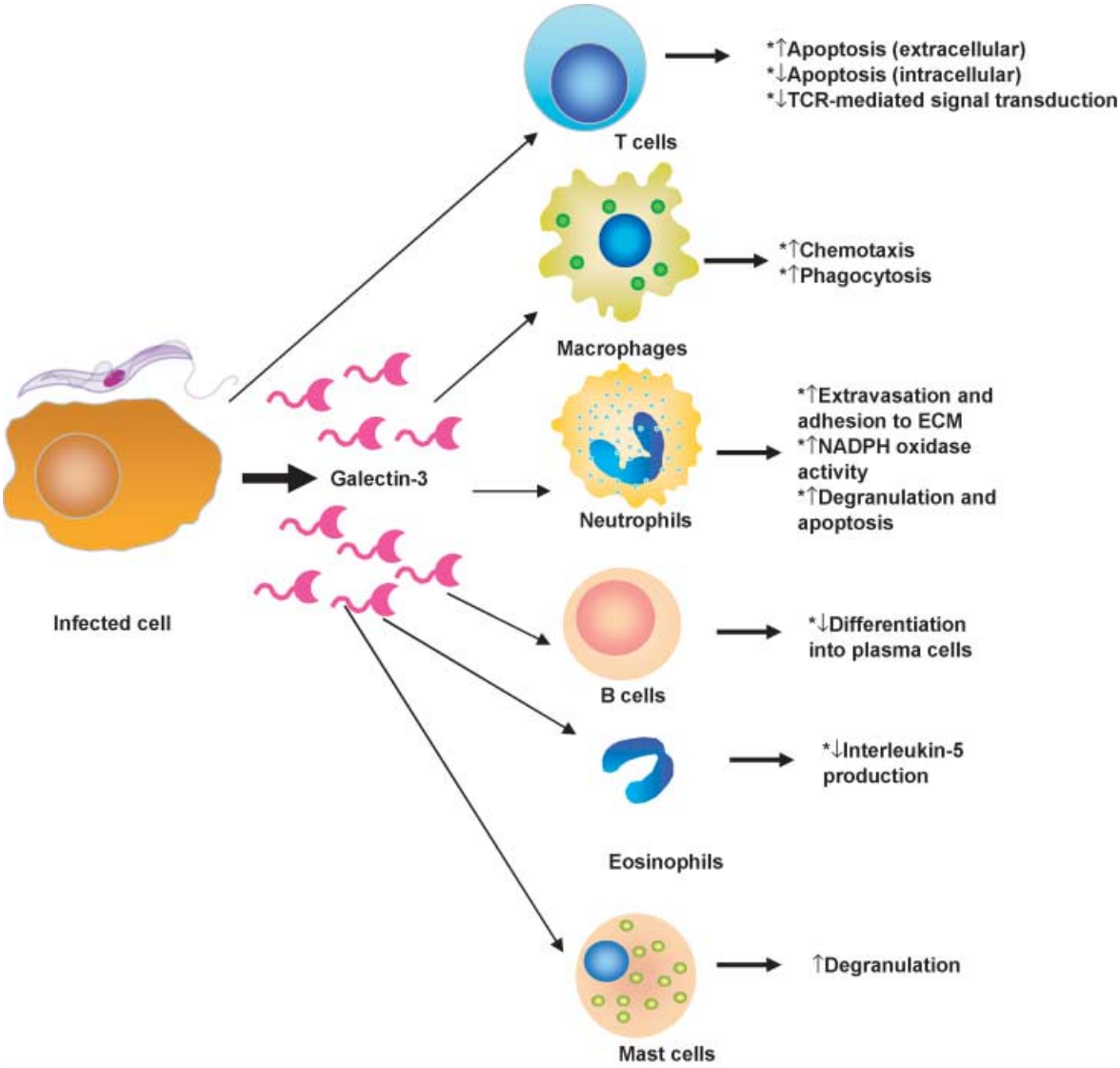

Figure 4 Influence of galectin-3 in the physiology of different immune cell types. Galectin-3 is up-regulated following infection with various infectious agents (details are provided in the text). This scheme illustrates the influence of galectin-3 secreted by infected cells in the physiology of T cells, macrophages, neutrophils, B cells, eosinophils and mast cells. Other galectins also contribute to immunoregulation but less is known about their biological effects. ECM: extracellular matrix.

Protozoa and viruses

Moody *et al*. (83) demonstrated that galectin-3 specifically binds to *T. cruzi* trypomastigotes and modulates adhesion of the parasite to extracellular matrix glycoproteins, such as laminin, in a carbohydrate-dependent manner (83). Recent findings from the same group showed that *T. cruzi* also uses galectin-3 to bind to human coronary artery smooth muscle cells (84).

Recently, Sato and colleagues (85) showed in a very elegant study that galectin-3 can interact with *Leishmania major* through binding to specific polygalactose epitopes on lipophosphoglycans (LPG). This interaction is species-specific, since galectin-3 does not bind to *L. donovani*, or to a *L. major* mutant that does not contain polygalactose epitopes on its LPG. In contrast, galectin-1 does not bind with significant affinity to *L. major*, indicating that the polygalactose epitope binds to the extended binding pocket of galectin-3, which is not present in galectin-1 (85). The same group further showed that galectin-9 can also recognize *L. major* by binding to the *L. major*-specific-polygalactosyl epitope (86). Frontal affinity chromatography using different lengths of poly β-galactosyl epitopes revealed that the affinity of galectin-9 for polygalactose is enhanced in proportion to the number of available [Gal-β1-3] units.

Even though galectins-3 and -9 have comparable affinities to polygalactosyl epitopes, only galectin-9 can promote the interaction between *L. major* and macrophages, suggesting distinctive roles for these galectins in the interactions of *L. major* with the infected host (85,86). In agreement with these findings, Cummings and colleagues recently showed that [GalNAc β1-4GlcNAc] (LacdiNAc)-glycans constitute a specific parasite pattern for galectin-3-mediated immune recognition (87). Thus, galectins may function as potential pattern recognition receptors (or dangers signals) transmitting the information of microbial invasion to immune cells. It is noteworthy, in this context, that galectin-1 has very recently been shown to promote adhesion of HIV-1 to the cell surface, thereby augmenting the efficiency of infection (88). The relevance of endogenous galectins in microbial invasion *in vivo* remains to be explored, for example in mice deficient for *galectin* genes.

Whereas the studies described above have focused on the interactions between mammalian galectins and pathogen glycans, it is also possible that pathogen-associated galectin-like molecules might contribute to microbial invasion or evasion of immune responses. One such galactose-binding protein has been described in tachyzoites of a virulent *Toxoplasma gondii* strain (89). This lectin, described as the micronemal protein 1 (MIC1), binds to type A human erythrocytes and this binding is inhibited by β-galactoside-related sugars, such as lactose (89).

Helminths

Helminth parasites may also express galectin-like molecules or may promote the up-regulation of galectins in infected tissues (reviewed in 14). Galectins, which show high similarity in their amino acid sequences, have been isolated from helminth parasites, including *Teladorsagia circumcincta* (90), *Haemonchus contortus* (91) and *Trichostrongylus colubriformis* (90). Furthermore, immunoblot analysis using antibodies raised against a galectin purified from *T. colubriformis* detected similar galectins in parasites from phylogenetically diverse families, including *Taenia serialis* and *Fasciola hepatica*, as well as a number of additional nematode species (14). These data indicate that helminth parasite galectins are probably evolutionarily conserved despite significant differences in parasite physiology, life cycles and tissue environments. At present no function has been attributed to galectins of parasitic helminths.

GALECTINS IN VECTOR–PATHOGEN INTERACTIONS

Insect galectins have been associated with embryonic development and with immunity against pathogens (92). Recently, Sacks, Valenzuela and colleagues (93) identified an insect galectin as the receptor for the *Leishmania* adhesin lipophosphoglycan (LPG); this interaction is critical for parasite survival in the midgut of its sand fly vector (93). Furthermore, analysis of the salivary gland transcriptome and proteome of the *Anopheles stephensi* mosquito revealed the presence of a novel secreted galectin, the function of which remains to be elucidated (94). The results presented in these studies open new avenues for research of insect immunity and demonstrate, at least in principle, the feasibility of exploiting receptors for parasite ligands as target antigens for transmission-blocking vaccines.

CONCLUSIONS AND FUTURE PERSPECTIVES

We have reviewed the multiple roles of galectins, a family of immunoregulatory β-galactoside-binding proteins, in the pathogenesis of viral, bacterial, fungal and parasitic infections. We have shown how galectins operate at different levels of both innate and adaptive immunity, by modulating immune cell survival, activation, differentiation and by interfering with the cytokine balance, and thus that it is very likely that these carbohydrate-binding proteins play a key role in the outcome of infectious diseases (Figure 2). Interestingly, and in contrast to previous assumptions, recent work clearly indicates that galectin family members are not redundant and that there are subtle but functionally relevant differences in the specificity of individual members of the family in their modulation of innate and adaptive immune responses.

The complexity of pathogen-encoded strategies for immune evasion has become increasingly obvious over the past few years, revealing the many interesting pathways used by pathogens to survive, expand and eventually be transmitted to new hosts. A major challenge in the future will be to demonstrate whether pathogenic microorganisms synthesize galectin-like molecules or regulate host galectins for their own benefit. Possible scenarios include immunosuppression through pathogen-mediated regulation of galectin gene expression or subversion of galectin-mediated signal transduction pathways, in order to prolong intracellular survival and prevent killing by immune effector cells. Thus, understanding the role of galectin–sugar interactions during infectious diseases might contribute to defining novel targets for candidate vaccines and for immune intervention.

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