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Review

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Roles of galectin-3 in immune responses

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Summary

Galectins are a family of animal lectins with conserved carbohydrate-recognition domains for β-galactoside. Galectin-3 is the only family member that is composed of a glycine/proline-rich N-terminal repeated sequence and a C-terminal carbohydrate-binding domain. Multiple functions of galectin-3 have been reported, depending on its location. Extracelluar galectin-3 can bind to cell surface through glycosylated proteins and thereby trigger or modulate cellular responses such as mediator release or apoptosis. Intracellular galectin-3 has been reported to inhibit apoptosis, regulate the cell cycle, and participate in the nuclear splicing of pre-mRNA. Recent studies have revealed that galectin-3 is expressed in a variety of cell types in the immune system, constitutively or in response to microbial invasion. These studies implicate galectin-3 in both innate and adaptive immune responses, where it participates in the activation or differentiation of immune cells. This review summarizes the roles of galectin-3 in the immune system and discusses the possible underlying mechanisms.

Key words: **galectin • galectin-3 • immunity • immune response**

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INTRODUCTION

The galectin family is defined by shared consensus amino-acid sequences and affinity for β-galactose--containing oligosaccharides[5]. This is an evolutionarily conserved family, and homologues exist in a wide variety of species in the animal kingdom, including sponges, nematodes[24], and humans[7]. To date, 15 galectins have been identified. These galectins can be grouped into three types: 1) proto-type (galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15), existing as monomers or homodimers consisting of one carbohydrate-recognition domain (CRD), 2) chimera-type (galectin-3), containing a non-lectin part connected to a CRD, and 3) tandem-repeat-type (galectin-4, -6, -8, -9 and -12), composed of two distinct but homologous CRDs in a single polypeptide chain. Galectin-3 was assigned various names in early studies, such as immunoglobulin E (IgE)-binding protein[29, 30, 45, 66], Mac-2 antigen[6, 66], CBP35[46], L-29[34], and L-34[43]. Polypeptide sequence analysis reveals that galectin-3 is composed of two domains: the N-terminal domain, which contains repeats of the consensus sequence PGAYPG, and the C-terminal CRD domain, which contains the NWGR consensus motif found also in the Bcl-2 family[68]. Interrupting the consensus sequence abrogates this domain's carbohydrate-binding activity as well as galectin-3's anti-apoptotic function[3]. Phosphoamino-acid analysis showed that serine 6 (about 90%) and serine 12 (about 10%) of the N-terminal of galectin-3 are phosphorylated[19]. Crystal structure study showed that, like other galectin CRDs, the C-terminal CRD domain of galectin-3 is composed of two anti-parallel β-sheets, one 5-stranded and the other 6-stranded, with the sugar-binding site formed by the amino-acid side chains of the 6-stranded β-sheet[20]. Galectin-3 in solution with an unoccupied CRD is monomeric, as determined by velocity sedimentation[37]. However, in the presence of a sugar substrate, galectin-3 precipitates as a pentamer[2], possibly due to self-association through the tandem repeats of the N-terminal domain[35].

Several recently published reviews discuss the extracellular[40] and intracellular[32] functions of galectin-3 in cancer diagnosis[33, 60, 62], thymocyte migration[54], innate immunity against infections[52], inflammation[4, 33, 48], and cell growth and apoptosis[69]. In this review we will focus on the roles of galectin-3 in the immune system.

GALECTIN-3 IN INNATE IMMUNE RESPONSES

Monocytes and macrophages

Galectin-3 was identified as the Mac-2 antigen, a surface marker highly expressed in thioglycollate-elicited macrophages. By pulse-chase analysis and subcellular fractionation studies, the Mac-2 protein was found both in the cytosol and in the extracellular medium[6]. Galectin-3 is also expressed in normal human peripheral blood monocytes and its level increases dramatically as human monocytes differentiate into macrophages upon culturing *in vitro*. Galectin-3 expression in human monocytes/macrophages is modulated by stimuli that cause their activation, such as lipopolysaccharide (LPS) and interferon (IFN)-γ. It is not known how galectin-3 expression is upregulated by monocyte/macrophage activation. It most likely involves NF-κB, a transcription factor with central roles in inflammation. Earlier studies have shown functional NF-κB binding sites in the promoter of galectin-3[18]. Secretion of galectin-3 from monocytes is stimulated by the calcium ionophore A23187, and soluble galectin-3 causes superoxide release from human monocytes. This activity depends on the lectin property of galectin-3, as it is inhibited by lactose. The authors postulated that galectin-3 may modulate the function of monocytes in an autocrine or paracrine fashion through binding to cell-surface glycoconjugates[31].

With the human promyelocytic leukemia cell line HL-60, Nangia-Makker et al.[39] showed that galectin-3 expression correlates with differentiation along the monocyte/macrophage, but not the neutrophil lineage. Treatment of THP-1 cells with phorbol 12-myristate 13-acetate (PMA) to stimulate macrophage differentiation also increases galectin-3 expression[25]. By using specific kinase inhibitors and co-transfection of galectin-3 reporter genes with constructs expressing components of signaling pathways, the authors found that the Ras/MEKK1/MKK1/AP-1 signal-transduction pathway plays an important role in the expression of galectin-3 in PMA-stimulated macrophages[25]. In atherosclerotic lesions, galectin-3 is expressed predominantly in foam cells and macrophages and rarely in the smooth muscle cells. The increased expression of galectin-3 in atherosclerotic lesions suggests its involvement in atherogenesis[38]. Kim et al.[25] further investigated the effect of modified lipoproteins on galectin-3 expression in macrophages and found that murine resident peritoneal macrophages loaded with acetylated low-density lipoprotein (LDL) or oxidized LDL showed increased galectin-3 protein and mRNA. These findings explain the enhanced expression of galectin-3 in atherosclerotic foam cells.

In elicited or activated macrophages, a significant portion (up to 30%) of galectin-3 is constitutively secreted[51]. Similar to what was observed with peripheral blood mononuclear cells[31], galectin-3 secretion

from these cells is stimulated markedly by calcium ionophore A23187. Only thioglycollate-elicited macrophages express cell-surface galectin-3, through binding to cell-surface carbohydrate structures[51]. Galectin-3 surface expression is markedly reduced upon activation of thioglycollate-elicited macrophages with LPS *in vitro*. The restricted cell-surface distribution of galectin-3 on thioglycollate-elicited peritoneal macrophages, a population of recently recruited monocytes, suggests that galectin-3 may be involved in early events of macrophage infiltration and tissue fixation such as extravasion and cell-matrix interactions[51].

There is ample evidence that galectin-3 mediates monocyte/macrophage migration. Sano et al.[50] showed that galectin-3 induced human monocyte migration *in vitro* and *in vivo* in a dose-dependent manner. Pertussis toxin (PTX) almost completely blocked monocyte migration induced by high concentrations of galectin-3. Galectin-3 caused a Ca^{2+} influx in monocytes, and both lactose and PTX inhibited this response. Cultured human macrophages and alveolar macrophages also migrated toward galectin-3. These results indicate that galectin-3 is a novel chemoattractant for monocytes and macrophages and suggest that the effect is mediated at least in part through a PTX-sensitive (G protein-coupled) pathway.

Several lines of evidence indicate that galectin-3 is important in macrophage phagocytosis. Galectin-3-deficient ($gal3^{-/-}$) cells exhibit reduced phagocytosis of IgG-opsonized erythrocytes and apoptotic thymocytes *in vitro*[49]. This protein is one of the component proteins of the phagosome[15]. Interestedly, one of the phagosome-associated proteins, alix, has been found to be a binding partner of galectin-3[32]. It has also been demonstrated recently that galectin-3 can mediate the recognition and phagocytosis of LDN-coated particles by macrophages[59]. In addition, galectin-3 has been shown to mediate the production of cytokines. It potentiates interleukin (IL)-1 production by human monocytes induced by LPS[21] and inhibits IL-5 expression in these cells[8].

Dendritic cells

Galectin-3 is highly expressed in the professional antigen-presenting cells, i.e. dendritic cells (DCs), and is able to mediate binding of DCs to lymphocytes[56]. Expression levels of galectin-3 as well as its ligand in DCs are elevated after infection with a parasite, and their interactions result in modulation of adhesion molecules and migration of the DCs[63]. Human keratinocytes produce galectin-3, which subsequently binds to the surface of Langerhans cells and modulates their binding to IgE glycoforms[65].

Neutrophils

Truong et al.[57] showed that galectin-3 is expressed in neutrophils and involved in IgE-dependent activation of neutrophils. Yamaoka et al.[67] showed that recombinant galectin-3 activates human neutrophils in a dose-dependent manner, an activity dependent on the lectin property intrinsic to its carboxyl-terminal domain. The amino-terminal domain is also necessary for this activity, as the carboxyl-terminal domain fragment alone fails to activate neutrophils, even though it retains the carbohydrate-binding property. Karlsson et al.[23] also found that galectin-3 is a potent activator of the NADPH-oxidase in exudated neutrophils, and the binding of galectin-3 to the surface of these cells is increased compared with neutrophils in the peripheral blood. The authors concluded that galectin-3 is a potent stimulus of the neutrophil respiratory burst, provided that the cells have first experienced an extravasation process[23].

Recruitment of neutrophils from blood vessels to sites of infection represents one of the most important elements of innate immunity. Movement of neutrophils across blood vessel walls to the site of infection first requires that the migrating cells firmly attach to the endothelial wall. Kuwabara and Liu[27] demonstrated that galectin-3 promotes adhesion of human neutrophils to laminin in a dose-dependent manner. The effect depends on both the lectin's carbohydrate-binding domain and its amino-terminal non-lectin region. Galectin-3-induced adhesion is significantly reduced by EDTA, although Ca^{2+} and Mg^{2+} are not required for its lectin activity. These results suggest a role for galectin-3 in the traversing of neutrophils through the basement membrane at sites of inflammation[27].

Using an *in vivo Streptococcal pneumonia* mouse model, Sato et al.[53] found that accumulation of galectin-3 in the alveolar space of *Streptococcus*--infected lungs correlates closely with the onset of neutrophil extravasation. They further showed that galectin-3 promotes neutrophil adhesion to endothelial cells *in vitro*, apparently as a result of direct cross-linking of neutrophils to the endothelium by galectin-3 because of its dependence on galectin-3 oligomerization. It appears that galectin-3 acts as an adhesion molecule to mediate neutrophil adhesion to endothelial cells during streptococcal infection. Accumulation of galectin-3 in lung, however, was not observed during neutrophil migration into alveoli induced by *Escherichia coli* infection, where the

majority of neutrophil emigration is known to be β2 integrin dependent. Based on these results, the authors propose that galectin-3 plays a role in β2 integrin-independent neutrophil extravasation during alveolar infection with *Streptococcus pneumoniae*[53].

Mast cells

Galectin-3 is present in variable amounts in several mast cell lines. The presence of galectin-3 on the surface of these cell lines is diminished to some extent by lactose, suggesting its attachment to yet unidentified glycoconjugates on the cell surface[12]. Galectin-3 has been shown to activate rat basophilic leukemia cells[13, 70].

Eosinophils

There is evidence that galectin-3 is expressed in eosinophils[58]. Dose-dependent inhibition by anti-galectin-3 monoclonal antibody (mAb) of IgE-dependent eosinophil-mediated cytotoxicity towards parasite targets suggests the role of this molecule in the function of human eosinophils[58]. Exogenous galectin-3 inhibits IL-5 expression in human eosinophils and the eosinophilic cell line EoL-3[8].

Interaction of galectin-3 with pathogens

It has been shown that galectin-3 binds to microbes at the site of infection. For example, the protozoal parasite *Trypanosoma cruzi* utilizes galectin-3 to adhere to laminin via surface glycoprotein[36]. *Leishmania major* also binds to galectin-3 through its surface lipophosphoglycans. This binding results in cleavage of galectin-3 and disruption of its oligomerization[42]. These kinds of interactions seem to be beneficial to microbes because they enhance microbial invasion and, in the meantime, may weaken galectin-3-mediated function in the defense against microbes, such as macrophage activation, neutrophil recruitment, and eosinophil-mediated cytotoxicity[58].

GALECTIN-3 IN ADAPTIVE IMMUNE RESPONSES

B cells

Galectin-3 is not expressed in resting B cells. However, its expression can be markedly induced by activation with IL-4 and CD40 cross-linking[1]. Activation with these stimuli promotes the survival and blocks the final differentiation of these cells, giving rise to a memory B cell phenotype. Galectin-3 is also expressed in B cells from *T. cruzi*-infected mice that receive signals for activation and differentiation *in vivo*[1]. By using an antisense strategy, the authors determined that galectin-3 is a critical factor that mediates the effects of IL-4 on B cell fate[1]. Galectin-3 was also found to express in diffuse large B cell lymphoma, primary effusion lymphoma, and multiple myeloma, but not in other lymphomas[17]. Ectopic expression of galectin-3 in these cells confers resistance to Fas-mediated apoptosis[17].

T cells

Thymocyte differentiation occurs in the context of the thymic microenvironment, in which T cell precursors interact with thymic microenvironmental cells and extracellular matrix. Villa-Verde et al.[61] showed that in the thymus, galectin-3 can be found mainly in the medulla and, to a lesser extent, in the cortex. The authors further showed that distinct microenvironmental elements, such as thymic epithelial cells, the epithelial component of thymic nurse complexes, and phagocytic cells of the thymic reticulum, produce, secrete, and accumulate galectin-3 on the cell surface. Recombinant galectin-3, as well as galectin-3--enriched medium, inhibited *in vitro* thymocyte interactions with thymic microenvironmental cells, accelerated the release of thymocytes from thymic nurse cells, and inhibited the reconstitution of these lymphoepithelial complexes[61]. These effects can be inhibited by lactose and by an anti-galectin-3 antibody. These data indicate that intrathymically produced galectin-3 acts as a de-adhesion molecule to modulate thymocyte/microenvironmental cell interactions[54, 61].

Similar to B cells, resting T cells do not express galectin-3. Galectin-3 expression can be induced by activation of T cells with anti-CD3 mAb or mitogen and enhanced by common γ-chain signaling cytokines, IL-2, IL-4, and IL-7, but not by the inflammatory cytokines tumor necrosis factor α and IFN-γ[22]. IL-2 deprivation and γ irradiation concomitantly down-regulate galectin-3 expression and T cell proliferation. Inhibition of endogenous galectin-3 expression blocked T cell proliferation, suggesting an important role for galectin-3 in the proliferation of activated T lymphocytes[22]. Addition of galectin-3 to Jurkat cells triggers a sustained influx of extracellular Ca^{2+} which is blocked by lactose, suggesting that galectin-3 released by accessory cells such as macrophages may also participate in Ca^{2+} signaling during T cell activation[11].

Galectin-3 is also reported to play a negative role in T cell activation, a process that requires clustering of a threshold number of T cell receptors (TCRs) at the site of antigen presentation. Galectin-3 was found to associate with the TCR complex on the cell surface. Deficiency in β1,6 N-acetylglucosaminyltransferase

V (Mgat5), an enzyme in the N-glycosylation pathway, abolishes galectin-3/TCR complex association, and in the meantime lowers T cell activation thresholds, with enhanced TCR clustering[10]. Pretreatment of wild-type T cells with lactose to disrupt galectin-3/TCR complex interaction produced a phenocopy of Mgat5$^{-/-}$ TCR clustering. These data indicate that galectin-3 interacts with Mgat5-modified glycans on the surface of T cells, thereby restricting TCR recruitment to the site of antigen presentation[10].

Galectin-3 is abundantly expressed in T cells infected with human T lymphotropic virus (HTLV)[18] and human immunodeficiency virus type 1 (HIV-1)[55]. Induction of galectin-3 expression involves the transactivator Tat in HTLV-1 and Tax in HIV. The role for galectin-3 in viral infection of T cells remains to be determined.

Data from our own research showed that under restrictive growth conditions, galectin-3 transfectants of the human leukemia Jurkat T cells exhibit higher growth rates than control transfectants which do not express this protein. Furthermore, galectin-3 expression in these cells confers resistance to apoptosis induced by anti-Fas antibody and staurosporine[68]. Galectin-3 was found to have significant sequence similarity with Bcl-2, a well-characterized suppressor of apoptosis[68]. In particular, the lectin contains the NWGR motif that is highly conserved among members of the Bcl-2 family and shown to be critical for the apoptosis-suppressing activity. We further demonstrated that galectin-3 interacts with Bc1-2 in a lactose-inhibitable manner, and concluded that galectin-3 is a regulator of cell growth and apoptosis and may function through a cell death inhibition pathway that involves Bcl-2[68].

On the other hand, secreted extracellular galectin-3 can signal apoptosis of human T leukemia cell lines and activated mouse T cells after binding to cell-surface glycoconjugate receptors through carbohydrate-dependent interactions. The apoptotic effect is dose dependent and inhibitable by lactose[14]. Cell lines that do not express endogenous galectin-3 are significantly more sensitive to exogenous galectin-3 than those that do express this protein, suggesting a cross-talk between the anti-apoptotic activity of intracellular galectin-3 and the proapoptotic activity of extracellular galectin-3. Indeed, galectin-3-transfected CEM cells were found to be more resistant to C(2)--ceramide-induced apoptosis than the control CEM cells[14]. Galectin-3's apoptosis-inducing effect is mediated by the cell surface receptors CD7 and CD29 (β1 integrin). Binding of galectin-3 to these cell surface receptors results in activation of mitochondrial apoptosis events including cytochrome c release and caspase-3 activation, but not caspase-8 activation[14]. Taken together, these results suggest that the induction of T cell apoptosis by secreted galectin-3 may play a role in the immune escape mechanism during tumor progression through the induction of apoptosis to cancer-infiltrating T cells, as is the case for galectin-1[47].

GALECTIN-3 IN ALLERGY AND AUTOIMMUNE DISEASES

It was shown that intranasal administration of galectin-3 DNA to rats results in reduced eosinophil infiltration and airway hypersensitive response[9]. This suggests a potential inhibitory role of extracellular galectin-3 in allergic airway disorders. However, we have recently found that galectin-3 was induced in the bronchoalveolar lavage fluid (BALF) in an allergic airway inflammation mouse model, and the allergic response was down-regulated in gal3$^{-/-}$ mice[71]. Staining of cell types in BALF that express galectin-3 indicated that macrophages are possibly the source of its expression[71]. Analysis of the cytokine in the BALF showed reduced Th2 cytokines in the gal3$^{-/-}$ mice. These results suggested the pro-inflammatory function of galectin-3 in the airway immune response. A recent report also suggests a stimulatory role of galectin-3 in inflammation. In an airway model for infection of *S. pneumoniae*, galectin-3 was induced in the BALF. Down-regulation of the airway response by administration of morphine decreased release of galectin-3 as well as chemokines and cytokines and resulted in less recruitment of neutrophils and increased susceptibility to *S. pneumoniae* infection[64]. The clinical action of galectin-3 has been studied in patients with age-associated atopic eczema/dermatitis syndrome[26]. In these patients, polymorphonuclear leukocyte-induce IgE secretion from B cells can be blocked by either lactose or a galectin-3 antibody, suggesting the involvement of galectin-3 in this process.

Galectin-3 expression is upregulated in synovial tissue from patients with juvenile idiopathic arthritis, which is characterized by hyperplasia of synovial cells and accumulation of mononuclear inflammatory infiltrates. This may account for the defective mononuclear apoptosis in synovial inflammatory infiltrates from patients with this disease[16]. Galectin-3 expression has also been correlated with disease activity in rheumatoid arthritis[41].

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of antinuclear antibodies. By serological analysis of a cDNA expression library (SEREX), Lim et al.[28] found that autoantibodies to galectin-3 are prevalent in the sera of patients with SLE, and those with polymyositis/dermatomyositis as well. These results suggest

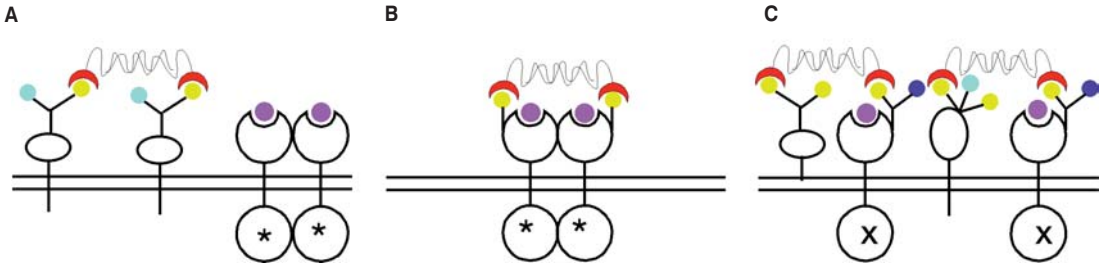

Figure 1. Effects of galectin-3 on the activation of immune cells by regulating cell surface receptor signaling. Binding of ligands (such as growth factors and cytokines) to their cognate receptors results in receptor clustering and activation. Galectin-3 is secreted out of the cell and bind to cell surface ligands. Such binding may have either positive or negative function on receptor signaling, depending on the specific receptors. **A** – galectin-3 binds to and sequesters receptor inhibitors, allowing for receptor dimerization and activation (*). **B** – galectin-3 directly crosslinks receptors and facilitate their activation. **C** – galectin-3 is tethered on the cell membrane in a network of glycoproteins including specific receptors and other glycoproteins. Such interactions restrict the mobility of the receptors and limit their clustering and activation after ligand binding.

that the presence of autoantibodies to galectin-3 is associated with renal disease[28].

The removal of degenerating myelin by phagocytosis is central to pathogenesis and repair in a traumatized and diseased nervous system. Reichert and Rotshenker[44] showed that galectin-3 expression is up-regulated, along with MAC-1 and F4/80, in the spinal cords and optic nerves of experimental allergic encephalomyelitis (EAE) mice in areas of demyelination and myelin degeneration, in myelin phagocytosing microglia and macrophages. Copolymer 1 (glatiramer acetate) concomitantly suppresses EAE, demyelination, and galectin-3 expression[44].

CONCLUSION

As illustrated in Figs. 1 and 2, the immune system provides a dynamic setting in which galectin-3 fully manifests its multi-functionality. It is one of the molecules utilized by immune cells to fend off pathogen invasion. On the other hand, some pathogens seem to be able to take advantage of this protein in the course of penetrating the defense system of the host. In addition, galectin-3 is important for the development and activation of cells involved in both the innate and adaptive immune responses. Regulation of life and death constitutes a significant part of its functions in these processes and this, too, can be employed by cancer cells in their attempts to escape the surveillance of the immune system.

While its involvement in macrophage migration and phagocytosis is fairly convincing, with data from knockout mice, other *in vitro* findings still need to be corroborated with similar animal models. At the molecular level, the basis for its multi-functionality awaits elucidation. It seems that this can be explained by its binding to distinct ligands inside the cell, on the cell surface or in the extracellular matrix, yet the identification of signals generated from such binding and their integration into known pathways leading to specific cellular responses remain a major task.

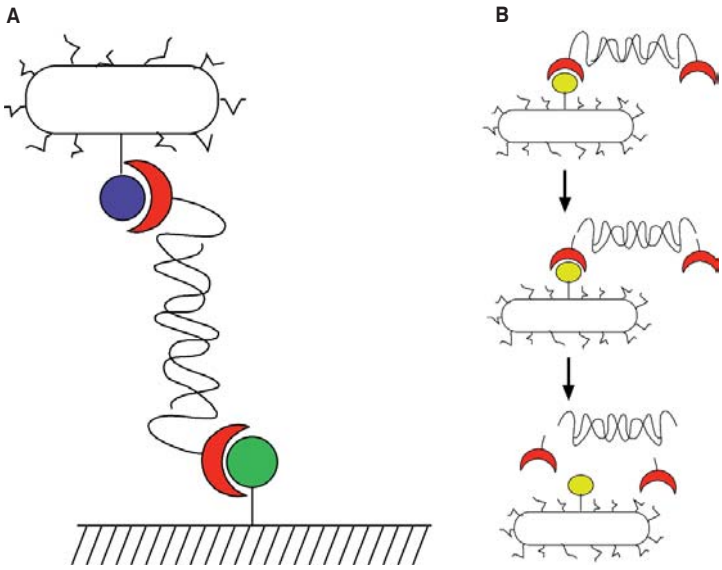

Figure 2. Pathogen/galectin-3 interactions during immune invasions. **A** – pathogens use galectin-3 to adhere to the basement membrane. In this process, galectin-3 cross-links glycoconjugates on the surface of pathogens and laminin on the basement membrane. **B** – inactivation of galectin-3 by pathogens such as *Leishmania major*, which binds to galectin-3 through its surface lipophosphoglycans. Such binding results in cleavage of galectin-3 and disruption of its self-association, and weakens galectin-3-mediated function in the defense against pathogens, such as macrophage activation, neutrophil recruitment, and eosinophil-mediated cytotoxicity.

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