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Galectin–glycan lattices regulate cell-surface glycoprotein organization and signalling

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Abstract

The formation of multivalent complexes of soluble galectins with glycoprotein receptors on the plasma membrane helps to organize glycoprotein assemblies on the surface of the cell. In some cell types, this formation of galectin–glycan lattices or scaffolds is critical for organizing plasma membrane domains, such as lipid rafts, or for targeted delivery of glycoproteins to the apical or basolateral surface. Galectin–glycan lattice formation is also involved in regulating the signalling threshold of some cell-surface glycoproteins, including T-cell receptors and growth factor receptors. Finally, galectin–glycan lattices can determine receptor residency time by inhibiting endocytosis of glycoprotein receptors from the cell surface, thus modulating the magnitude or duration of signalling from the cell surface. This paper reviews recent evidence *in vitro* and *in vivo* for critical physiological and cellular functions that are regulated by galectin–glycoprotein interactions.

Keywords

apoptosis; endocytosis; galectin; glycoprotein; lattice; lipid raft

Introduction

Organization of the plasma membrane of all types of cells is a fundamental process that controls the cell's response to stimuli. Thirty years ago, the fluid mosaic model of the membrane suggested that integral membrane proteins are dispersed in a relatively uniform fluid lipid bilayer [1]. A more recent picture of the plasma membrane presents a dynamically structured mosaic model, in which membrane proteins are compartmentalized or clustered into non-random discrete domains. This compartmentalization correlates well with recent discoveries in cell signalling. A current model states that the cohesive forces that maintain protein assemblies at the cell surface include lipid–lipid, protein–protein and protein–lipid interactions [2,3]. However, while virtually every cell-surface protein is glycosylated, these models do not take into account the role of glycans in plasma membrane organization. In particular, the cell surface, or plasmalemmal, glycoproteins that relay signals from the outside to the inside of the cell must be organized into functional domains for efficient and appropriate cellular responses to occur.

By binding to specific glycans on plasmalemmal glycoproteins, oligomeric glycan-binding proteins (lectins) help to organize glycoprotein assemblies on the surface of the cell [4–7]. These lectin–glycoprotein lattices are characterized by multiple low-affinity interactions, and the strength of the interactions can be dynamically modulated by altering protein glycosylation

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or lectin expression [8]. Such lectin–glycoprotein lattices may create homotypic or heterotypic glycoprotein complexes that can regulate a variety of cell functions, including proliferation, migration and apoptosis [7,9].

One family of multivalent lectins that can organize cell-surface microdomains or lattices is the galectins [7]. The galectins are a family of animal lectins that share a common CRD (carbohydrate recognition domain). There are structural subfamilies of galectins, but all galectins form higher order multimers and can thus cross-link glycan ligands. The 14 mammalian galectins are all made in the cytosol, and many are secreted from the cell by a non-classical secretion pathway [10]. While galectins are soluble proteins with no transmembrane domains, secreted galectins stay associated with the cell surface by binding cell-surface glycoproteins, where the interaction of multivalent lectins with multivalent glycan ligands can create these lattices [11,12].

To date, there are three major roles played by galectin–glycoprotein lattices in regulating cell function. The first is the role of galectin lattices in organizing membrane domains, as seen in lipid raft formation and apical protein targeting. The second is the role of galectin lattices in regulating the signalling threshold at the cell surface exemplified by T-cell antigen recognition and T-cell apoptosis. Finally, galectin lattices can determine receptor residency time at the cell surface by inhibiting endocytosis, as seen in tumour cell signalling via growth factor receptors and pancreatic cell sensing of glucose (Table 1). This review highlights the important roles that galectin lattice formation plays *in vivo* by examining numerous recent publications that show that eliminating the galectin lattice, either by taking away the galectin or by removing the glycan from cell-surface proteins, can lead to cellular dysfunction or disease states.

Organizing membrane domains

Lipid rafts

Plasma membrane ‘lipid rafts’ are microdomains enriched in certain lipids and proteins that have been proposed to participate in many different cell signalling processes. Early studies found that certain membrane proteins were enriched in cholesterol-dependent, detergent-insoluble fractions that corresponded to submicron-sized domains on the cell surface [13]. The lipid raft model has proposed that recruitment of various proteins to these microdomains, as well as assembly of the submicron-sized domains into larger complexes, facilitates biological responses to extracellular signals in a variety of cell types [14].

Proteomic analysis of cholesterol-enriched membrane domains isolated from intestinal cell microvillar membranes revealed galectin-4 as the most abundant protein in this fraction [15]. Initially, galectin-4 was regarded simply as a ‘marker’ of the lipid raft fraction from these cells. However, Danielsen and co-workers [15] found that lactose treatment of isolated lipid raft membrane fractions from intestinal cell microvilli resulted in both the release of galectin-4, as well as release of integral membrane raft glycoproteins, such as alkaline phosphatase and aminopeptidase N. This result suggests that galectin-4 acts as a raft stabilizer or organizer, retaining the different glycoproteins in these microdomains in a carbohydrate-dependent manner. This group proposed that galectin-4 bound to glycans on the lipid raft glycoproteins, such as alkaline phosphatase and aminopeptidase N, to form a glycan-dependent lattice that stabilized lipid raft formation.

Recent work on osteoblast proliferation supports this model of galectin–glycan stabilization of plasma membrane microdomains: Tanaka and co-workers [16] found that galectin-9 induced proliferation of human osteoblasts in a dose-dependent manner. This osteoblast proliferation was accompanied by clustering of lipid rafts on the cell surface and downstream phosphorylation of c-Src and ERK1/2 (extracellular-signal-regulated kinase 1/2). Disruption

of galectin-9-induced raft association by treatment with β-methylcyclodextrin reduced c-Src phosphorylation and cell proliferation [16]. These two studies suggest that lipid raft stabilization is promoted by galectin-induced lattice formation. A closer examination of glycosylated raft proteins, specifically identifying galectin-binding glycoproteins, may reveal further evidence for this model.

Apical targeting

Organizing membrane domains is especially important in polarized epithelial cells. Specific sorting signals can target certain proteins and groups of proteins to either the apical or the basolateral plasma membranes. Early studies have implicated N-glycans as a feature that facilitates apical targeting of specific glycoproteins [17]; however, later studies examining the effect of removing N-glycans from specific glycoproteins on apical targeting have revealed conflicting results, as glycosylation appears critical for sorting some, but not all, glycoproteins [18]. One model of apical sorting proposed that an unknown lectin would regulate apical sorting of glycoproteins [18]; recent data suggest that one such lectin may be a galectin.

Post-Golgi-enriched fractions of MDCK (Madin–Darby canine kidney) epithelial cells revealed the presence of galectin-3 associated with apically targeted vesicles [19]. Galectin-3 was found on the luminal side of apical vesicles, 5 min after vesicle release from the *trans*-Golgi network. In these cells, galectin-3 co-purified with LPH (lactase–phlorizin hydrolase) and other apically targeted glycoproteins, which appear to associate in a non-lipid raft-dependent manner. Depletion of galectin-3 from MDCK cells by RNAi (RNA interference) resulted in missorting of these apical proteins to the basolateral membrane compartment. Moreover, treatment of membrane fractions with lactose, but not other non-ligand saccharides, dissociated galectin-3 from LPH, p75 and gp114 (glycoprotein 114), three glycoproteins found in apically targeted vesicles. These results suggested that galectin-3 recognizes specific apically targeted glycoproteins and stabilizes vesicular association of these glycoproteins through formation of a galectin–glycan lattice.

Studies in the galectin-3-null mouse have confirmed the critical role of galectin-3 in apical membrane sorting [20]. *In vivo*, the intestinal brush border hydrolases LPH and DPPIV (dipeptidyl peptidase IV), which are expressed by polarized intestinal enterocytes, bind to galectin-3. In intestinal enterocytes of galectin-3-null mice, both of these apical hydrolases were mislocalized to the basolateral membrane. In addition, enterocytes from throughout the small intestine in galectin-3-null animals showed other membrane abnormalities and intracellular accumulation of LPH.

While galectin-3 participates in apical sorting of non-raft-associated glycoproteins, lipid rafts have also been proposed to play a role in the targeting of proteins to the apical membrane; it appears that galectins are involved in this process as well. In HT-29 5M12 (enterocytelike) cells, galectin-4 was found in post-Golgi vesicles and was a major component of the detergent-resistant membrane fraction. Depletion of galectin-4 in these cells by RNAi resulted in the intracellular accumulation of apical membrane glycoproteins, as well as reduced apical delivery of these glycoproteins [21]. Collectively, these data reveal a critical role for galectins in the organization of various types of membrane domains, both raft and non-raft, and demonstrate that galectin–glycan lattices are important for targeting of apical transmembrane glycoproteins both *in vitro* and *in vivo*.

Regulating signalling thresholds

Regulation of cell death is critical for proper T-cell development in the thymus, to eliminate self-reactive T-cells, to elicit an appropriate T-cell response in the periphery, and to eliminate activated T-cells after pathogens are cleared. Thus misregulation of lymphocyte apoptosis can

result in autoimmune disease and neoplastic lymphoid proliferation [22]. T-cell death can be controlled by external signals that are relayed via cell-surface glycoproteins. Galectin interaction with T-cell glycoproteins is one possible mechanism of control during T-cell apoptosis, by setting a signalling threshold that is dependent on galectin lattice formation.

T-cell death

Early studies on galectin-1 and T-cells revealed that galectin-1 is expressed in the thymus, lymph nodes, and at various sites of T-cell death, such as inflamed tissue [23,24]. Recombinant galectin-1 induced apoptosis of activated T-cells *in vitro* [25], and also induced apoptosis of specific thymocyte subsets that typically undergo non-selection or negative selection *in vivo* [26,27]. Galectin-1 bound to a restricted set of T-cell surface glycoproteins, including CD3, CD7, CD43 and CD45. Cell-surface localization studies revealed that galectin-1 binding to T-cells caused a dramatic redistribution of these glycoproteins during cell death, with CD45 and CD3 co-localized on apoptotic blebs containing externalized phosphatidylserine (an early marker of apoptosis), while CD7 and CD43 co-localized away from the membrane blebs [28]. Moreover, the clustering of CD45 on apoptotic blebs could be positively or negatively regulated by the presence of binding or blocking glycan ligands on CD45 [29–31]. These same glycan ligands are differentially expressed by distinct thymocyte subsets, correlating with subset susceptibility to galectin-1 death [24,29]. Similarly, differential glycosylation of CD45 was recently found to modulate susceptibility of Th1, Th2 and Th17 cells to galectin-1 cell death [32]. These data support a model in which galectin-1 binds to specific glycan ligands on a subset of cell-surface glycoproteins to segregate the glycoproteins into discrete domains and initiate T-cell death. This model implies that a T-cell can alter the threshold of cell signalling and thus alter downstream responses by changing glycosylation of cell-surface glycoproteins. These results have significant *in vivo* relevance.

TCR (T-cell receptor) stimulation and T-cell development

TCR stimulation on developing thymocytes by antigens displayed on thymic epithelial cells and APCs (antigen presenting cells) regulates thymocyte maturation and death, via parallel processes termed positive and negative selection. High-affinity binding of TCRs to self-antigens induces thymocyte death through negative selection, whereas minimal activation by low-affinity binding of antigen to the TCR is required for positive selection. Therefore the magnitude of the TCR signal determines T-cell fate during development.

Galectins have been shown to modulate the threshold of TCR signalling. Galectin-1 selectively amplified certain TCR signals; Miceli and co-workers [33] found that addition of exogenous recombinant galectin-1 to murine T-cells *in vitro* co-operated with TCR engagement to induce T-cell apoptosis. In addition, galectin-1 inhibited TCR-induced interleukin-2 production and proliferation of primary mouse thymocytes. These data indicated that galectin-1 would enhance negative selection and reduce positive selection, suggesting that galectin-1 is a potent modulator of TCR signals. Recent *in vivo* work confirmed this prediction. Using galectin-1-null mice crossed on to different TCR transgenic mouse models, the Miceli group found that loss of galectin-1 expression promoted positive selection and reduced negative selection during thymocyte development *in vivo* by modulating TCR signalling. They concluded that galectin-1 promotes thymocyte negative selection *in vivo* by increasing TCR signalling through galectin lattice stabilization of agonist–antigen complexes with the TCR [34]. Supporting a role for galectin-1 in promoting negative selection is the observation that galectin-1-null mice, which would be proposed to have reduced negative selection in response to self-antigens, have enhanced susceptibility to autoimmune disease [32].

Demetriou et al. [35] have also proposed a role for galectin-3 in regulating TCR signalling during T-cell response to antigen. This group has analysed *Mgat5*-null mice that lack specific

N-glycan branches that are preferentially recognized by galectins. Loss of this glycan branch reduced galectin-3 association with TCRs on T-cells, and resulted in altered TCR signalling and downstream calcium flux in the cells [35,36]. These glycan-deficient mice also demonstrated increased susceptibility to autoimmune disease and alterations in T-cell cytokine production [35,37,38], supporting a role for galectin-3 interactions with TCRs in regulating response to antigen.

Collectively, these data reveal a critical role for galectins in the regulation of T-cell signalling thresholds, mediated through multiple different cell-surface receptors including CD45, CD43 and the TCR, and demonstrate that galectin–glycan lattices are important for proper T-cell development and appropriate response to antigens.

Receptor residency time at the cell surface

The ability of a cell to flexibly and quickly react to the extracellular environment is mediated through interactions of cell-surface receptors with cognate ligands. One mechanism of regulating this complex process is the removal of receptors from the cell surface by endocytosis, to diminish the magnitude or duration of a cell signalling event. Often, ligand binding to a receptor can trigger endocytosis. For example, GPCRs (G-protein-coupled receptors) are down-regulated following ligand-induced activation by endocytic trafficking to lysosomes [39], and ligand–receptor complexes of EGF (epidermal growth factor) and EGFR (EGF receptor) are endocytosed through clathrin-coated pits for degradation [40]. Conversely, increasing the residency time of a receptor on the cell surface can increase the magnitude or duration of signalling by that receptor. Thus one could imagine that mechanisms that inhibit receptor endocytosis would lead to stronger or more prolonged signalling. Many membrane receptors are variably glycosylated, and numerous mutational studies have revealed that glycosylation is critical for proper receptor signalling function [41]. Formation of galectin lattices with cell-surface receptors could inhibit receptor endocytosis and prolong signalling, and indeed recent data would suggest that this model is accurate.

Growth factor receptors and cancer cells

The *Mgat5* gene encodes the β1,6N-acetylglucosaminyl-transferase V, a Golgi-localized enzyme that participates in N-glycan synthesis and initiates formation of polylactosamine sequences on N-glycans that can be recognized by galectins [42]. *Mgat5* expression is up-regulated in carcinomas and *Mgat5* deficiency suppresses cancer progression in certain mouse models [43]. Partridge et al. [4] tested the hypothesis that *Mgat5*-modified N-glycans oppose growth factor receptor endocytosis in tumour cells by promoting formation of cell-surface galectin lattices, resulting in prolonged growth factor signalling in tumour cells. In this study, *Mgat5*-deficient cells showed reduced sensitivity to EGF signalling. Moreover, galectin-3 was co-localized with EGFR in wild-type cells, but not in *Mgat5*-deficient cells. Treatment of wild-type cells with lactose, to remove cell-surface galectins, dampened the cellular response to EGF, suggesting that loss of galectins reduced the cell-surface density of EGFRs. Additionally, *Mgat5*-deficient cells displayed increased intracellular co-localization of EGFR with an endosomal marker compared with wild-type cells, a phenotype that was mimicked by treating wild-type cells with lactose, providing evidence that EGFRs are maintained at the cell surface by a galectin lattice.

Further studies revealed that competition between the galectin lattice and oligomerized caveolin-1 microdomains (that mediate endocytosis) regulates EGFR localization and thus the magnitude of EGFR signalling in tumour cells [44]. This study used FRAP (fluorescence recovery after photobleaching) to demonstrate that EGFR movement to endocytic vesicles is reduced in wild-type cells compared with *MgatV*-deficient cells, presumably due to galectin lattices retaining growth factor receptors on the cell surface.

Glut2 (glucose transporter 2) receptor and diabetes

Cell-surface expression of Glut2 is critical for pancreatic *β*-cell function. Glut2 is N-glycosylated, and N-glycosylation has been shown to be critical for the function of other Glut family members [45]. The GnT-4a glycosyltransferase, encoded by *Mgat4a*, is critical for proper N-glycosylation of Glut2 in pancreatic *β*-cells. Ohtsubo et al. [46] showed that *Mgat4a*-deficient mice had impaired glucose transport and insulin secretion by *β*-cells, resulting in Type 2 diabetes *in vivo*. Histological examination of *Mgat4a*-deficient mice showed intracellular localization of Glut2 receptors, suggesting that increased endocytosis of the transporter occurred in the absence of proper N-glycosylation [46]. These *in vivo* assays support the model in which galectin lattice formation with cell-surface receptors inhibits or reduces receptor endocytosis. While galectin-9 was identified in these cells, additional experiments are required to determine the precise galectin or galectins mediating retention of Glut2 on the pancreatic *β*-cell surface.

Collectively, these data reveal a critical role for galectins in the regulation receptor residency time at the cell surface, by inhibiting endocytosis through formation of a galectin–glycoprotein lattice. These experiments demonstrate that galectin–glycan lattices can play critical roles *in vivo* in tumorigenesis and diabetes.

Conclusions

It is clear that several critical physiological and cellular functions can be regulated by galectin–glycoprotein interactions. Consequently, cells may ‘fine-tune’ the regulation of these functions, beyond simply regulating expression of receptors and ligands, by modulating galectin expression and/or glycoprotein glycosylation. Galectin binding specifically regulates particular biological events, including organizing membrane domains, setting signalling thresholds, and increasing receptor residency time at the cell surface, by responding to changes in cellular glycosylation; support for this model is provided by the observation that loss of specific glycans in genetically modified mice results in loss of galectin lattice formation, with distinct *in vivo* consequences [4,35–38,46].

Recent data have suggested that galectin–glycoprotein lattices may also play important roles in the pathogenesis of infectious disease. This is not altogether surprising, considering pathogens (fungi, bacteria and viruses) are also covered by multivalent glycans that can bind host galectins. For example, syncytia formation of cells expressing Nipah virus attachment (G) and fusion (F) glycoproteins is inhibited by galectin-1, and soluble Nipah G and F glycoproteins form higher order oligomers in the presence of galectin-1, suggesting that a galectin lattice is involved in inhibition of viral-mediated cell fusion [47]. Multivalent galectins have also been shown to enhance parasite binding to host cells, such as *Trypanosoma cruzi* attachment to endothelial cells via galectin-3, *Leishmania major* binding to macrophages via galectin-9, and HIV attachment to T-cells via galectin-1 [48–50]. Understanding the roles of galectins in host–pathogen interactions represents an exciting new area of research in the field of infectious disease.

While many of the experiments described in this review provide evidence for galectin–glycoprotein lattices on the cell surface, further studies are needed to visualize the galectin lattice and to understand the structural features regulating lattice assembly/disassembly. Microscopic techniques, such as FRAP will be useful to examine the effect of galectin lattices on glycoprotein movement on the cell surface. Another critical question concerns the size of the minimal lattice domain that is required for specific effects. For example, is a larger lattice required for lipid raft stabilization versus regulation of T-cell signalling? Advances in microscopy and novel techniques for fluorescent glycoprotein labelling will help to illuminate the answers to these questions.

Galectin lattice formation creates an additional level of molecular regulation at the cell surface that can be rapidly and easily controlled. The low-affinity/high-avidity interactions of multivalent galectins with multivalent glycoproteins can dynamically modulate cellular signalling, setting signalling thresholds and acting as a rheostat to fine-tune cellular responses.

Note added in proof (received 3 October 2008)

A recent study has demonstrated that a galectin-1 lattice is responsible for retaining the renal epithelial Ca^{2+} channel TRPV5 at the plasma membrane, providing evidence for galectin lattice-mediated regulation of ion balance via regulation of channel residency at the cell surface [51].

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Abbreviations used

EGF	epidermal growth factor
EGFR	EGF receptor
FRAP	fluorescence recovery after photobleaching
Glut2	glucose transporter 2
LPH	lactase–phlorizin hydrolase
MDCK	Madin–Darby canine kidney
RNAi	RNA interference
TCR	T-cell receptor

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Table 1
Galectin–glycoprotein lattices that regulate cell functions

Shown are galectin receptor glycoproteins that have been proposed to participate in lattice formation. This does not constitute a comprehensive list of galectin-binding glycoproteins. DPPIV, dipeptidyl peptidase IV; gp114, glycoprotein 114; MUC1, mucin 1.

Galectin	Cell types affected	Glycoprotein receptors	Functions	References
1	T-cells, thymocytes	CD3/TCR, CD7, CD43, CD45	Apoptosis, regulate antigen response	[23–29]
3	MDCK (renal epithelia), intestinal enterocytes, T-cells, carcinoma cells	MUC1, LPH, p75, gp114, DPPIV, TCR, EGFR	Stabilize apically targeted vesicles, regulate response to antigen, inhibit growth factor receptor endocytosis	[4,11,19,20,35–38,44]
4	Intestinal cell microvilli, HT-29 5M12 (enterocyte-like cells)	Alkaline phosphatase, aminopeptidase N	Lipid raft stabilization, lipid raft-dependent apical targeting	[15,21]
9	Osteoblasts, pancreatic β-cells	Glut2	Lipid raft stabilization, inhibit Glut2 endocytosis	[16,46]