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Critical Review

Dissecting the Signal Transduction Pathways Triggered by Galectin–Glycan Interactions in Physiological and Pathological Settings

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Summary

Galectins are a family of evolutionarily conserved animal lectins with pleiotropic functions and widespread distribution. Fifteen members have been identified in a wide variety of cells and tissues. Through recognition of cell surface glycoproteins and glycolipids, these endogenous lectins can trigger a cascade of intracellular signaling pathways capable of modulating cell differentiation, proliferation, survival, and migration. These cellular events are critical in a variety of biological processes including embryogenesis, angiogenesis, neurogenesis, and immunity and are substantially altered during tumorigenesis, neurodegeneration, and inflammation. In addition, galectins can modulate intracellular functions and this effect involves direct interactions with distinct signaling pathways. In this review, we discuss current knowledge on the intracellular signaling pathways triggered by this multifunctional family of β-galactoside-binding proteins in selected physiological and pathological settings. Understanding the "galectin signalosome" will be essential to delineate rational therapeutic strategies based on the specific control of galectin expression and function.

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Abbreviations CRD, Carbohydrate-recognition domain; Src, Src tyrosine kinase; JNK, c-Jun N terminal kinase; FAK, focal adhesion kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; CREB, cAMP response element binding protein; PI3K, phosphatidylinositol 3 kinase; PPARγ, peroxisome proliferator-activated receptor-γ; C/EBP β/α, CCAAT/enhancer-binding protein; PKC, protein kinase C; PKA, protein kinase A; ROS, reactive oxygen species; WASp, Wiscott Aldrich Syndrome protein.

INTRODUCTION

Glycans are molecular arrangements abundantly and broadly exposed in mammalian cells as a part of glycoproteins and glycolipids. These carbohydrate structures, which collectively constitute the so-called "glycome" are substantially altered as a dynamic response of cells to a wide-range of physiological and pathological stimuli (*1*). This complex assortment of cell surface saccharide structures is finely regulated by the activity of a number of glycosyltransferases and glycosidases acting sequentially and determining the "glycosylation signature" of different cells and tissues. The responsibility of decoding this biological information is assigned, at least in part, to endogenous glycan-binding proteins or lectins, including C-type lectins, siglecs, and galectins (*1*). Galectins, a family of animal lectins, widely distributed in the animal kingdom recognize multiple *N*-acetyllactosamine units present on cell surface glycoproteins and glycolipids (*2*). Crystal structure of most galectins has been determined showing that these proteins contain at least one conserved domain of around 130 amino acids designated as the carbohydrate-recognition domain (CRD) that is responsible for their carbohydrate-binding properties (*1*). Based on their structure, galectins are classified into different groups: (*a*) the "prototype" subfamily (galectins-1, -2, -5, -7, -10, -11, -13, -14, and

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-15), which contains one CRD; (*b*) the "tandem-repeat" subfamily (galectins -4, -6, -8, -9, and -12), which contains two CRDs and (*c*) the "chimera-type" (galectin-3), which is comprised of an unusual proline- and glycine-rich domain adjacent to the CRD (*1*). Most "proto-type" galectins can form dimers through noncovalent interactions, whereas "tandem-repeat-type" galectins are constitutively bivalent. On the other hand, the chimera type galectin-3 can form pentamers in the presence of multivalent ligands (*2*). This ability to oligomerize is essential for crosslinking cell surface glycoproteins and conveying extracellular information into distinct signaling events that control multiple biological responses (*2*).

In general, galectins are soluble proteins and have features typical of cytoplasmic molecules. However, their localization is not limited to the cytoplasm; they are also found in the nucleus, on the cell surfaces, and even in the extracellular space (*1, 2*). Yet, regardless of their localization, these widely distributed proteins have been shown to be involved in the regulation of many cellular processes (*1–3*). In some cases, this regulation involves the direct control of cellular differentiation and activation by acting as "on-and-off" switches that control specific transcriptional activities. In other cases, galectin-mediated regulation involves fine control of the mechanisms of cell survival, growth, and transformation (*3*). This review summarizes our current knowledge on the intracellular signaling pathways triggered by galectins in physiological processes (with emphasis on the differentiation and function of hematopoietic cells) and pathological conditions associated with tumor progression.

GALECTINS IN THE PHYSIOLOGY OF NORMAL TISSUES

This section summarizes some of the intracellular signaling events elicited by galectin–glycan lattices in selected physiological settings (Table 1).

Embryogenesis

Galectins are expressed during embryogenesis in a coordinated manner and influence several developmental processes. Although early studies suggested that mice genetically deficient in galectins lack an evident phenotype (*19*), recent reports have challenged these early observations demonstrating several defects in mice deficient in individual members of the family (*2*). Galectin-1 has been shown to regulate the proliferation of embryonic cells via specific interactions with the Fos B transcription factor (*4*). This effect appears to be independent of the lectin properties of this protein and involves the participation of amino acid residues 25–30, a region joined by two internal β-strands and relatively closed to the N-terminus of the protein (*20*). In addition, galectin-15 has been implicated in blastocyst growth, elongation, and implantation. These biological functions were found to be dependent on the integrin-binding activity of this lectin and signaling through c-Jun N-terminal kinase (JNK) (*5*).

Connective Tissues

The shape and nature of the connective tissue are strongly influenced by galectins. Differentiation and proliferation of primary preadipocytes is dependent on galectin-3 and galectin-12 through involvement of CCAAT/enhancer-binding protein (C/EBP-β, α), peroxisome proliferator-activated receptor (PPAR-γ), Akt, extracellular signal-regulated kinase (ERK), and cAMP response element-binding protein (CREB) (*6, 7*). Interestingly, galectin-3 plays an essential role in fetal bone and cartilage formation, probably as a result of matrix metalloproteinase (MMP)-9 signaling (*21*). The bone remodeling function of this "chimera-type" lectin is also present during adult periods of life and is regulated by the Runt family of transcription factors (*8*). Notably, osteoblast proliferation is regulated by galectin-9 through activation of the c-Src/ERK signaling pathway (*9*).

Muscle, Skin, and Endothelium

Galectin-1 participates in the myogenic conversion of mesenchymal stem cells and muscle-derived fibroblasts (*10*) through a mechanism that remains poorly understood. Processes of skin formation and repair are also modulated by galectins. Increased apoptosis in galectin-3-deficient keratinocytes was found to be associated with higher ERK and lower Akt activation following UVB irradiation (*11*). On the other hand, contrasting results have been reported concerning the role of galectin-7 in keratinocyte behavior (*12, 13*). Galectin-7 is upregulated in UVB-irradiated epidermal keratinocytes, and ectopic expression of galectin-7 made these cells more susceptible to undergo apoptosis (*12*). However, this proapoptotic function has recently been challenged by observations in galectin-7-deficient mice in which this "proto-type" galectin could protect keratinocytes from irradiation-induced cell death (*13*). These apparent discrepancies could be explained by the different levels of galectin-7 attained following overexpression of this protein or under physiological conditions *in vivo* or by considering a biphasic effect of galectin-7 on keratinocyte behavior depending on different kinetic parameters. Yet, more studies are required to explain such experimental discrepancies that affect the functions of most members of the galectin family.

Galectin-1 has been demonstrated to be mitogenic for vascular endothelial cells. It interacts with the β_1 subunit of integrin on vascular smooth muscle cells and induces tyrosine phosphorylation of the focal adhesion kinase (FAK) (*15*). Likewise, galectin-3 interacts with $\alpha_3\beta_1$ integrin on the cell surface of endothelial cells (EC) and with NG2 proteoglycans expressed by microvascular pericytes in newly-formed blood vessels. This multimolecular interaction plays an important role in EC motility and neovascularization and is associated with FAK and ERK1/2 phosphorylation (*16*).

Neural Tissue

Galectins also participate in the development and maintenance of function of neural tissues. Galectin-1 induces astrocyte

Table 1
Galectin-mediated signaling pathways in nonhematopoietic tissues

Tissue/Cell	Function	Galectin member	Signaling pathway	Refs.
Embryonic cells blastocyst	Cell cycle arrest	Galectin-1	FosB	(*4*)
	Growth/implantation	Galectin-15	JNK	(*5*)
Connective tissue	Adipocyte proliferation	Galectin-3	?	(*6*)
	Adipocyte differentiation	Galectin-12	C/EBP $\alpha\beta$, PPARγ, Akt, ERK, CREB	(*7*)
Cartilage/Bone	Bone modelling	Galectin-3	Runt	(*8*)
	Osteoblast proliferation	Galectin-9	c-Src, ERK	(*9*)
Muscle	Myogenic function	Galectin-1	?	(*10*)
Epidermis	Skin formation and keratinocyte repair	Galectin-3	ERK	(*11*)
		Galectin-7	p53, JNK, cytochrome c, caspase-3, ROS	(*12–14*)
Endothelium	Vascular smooth muscle cell adhesion	Galectin-1	FAK	(*15*)
	Neovascularization	Galectin-3	FAK, ERK1/2	(*16*)
Neural tissue	Astrocyte differentiation	Galectin-1	DeltaFosB	(*17*)
	Neuronal differentiation	Galectin-3	RAS, MAPK	(*18*)

differentiation and fosters the ability of these cells to secrete brain-derived neurotrophic factor (BDNF), which in turn promotes neuronal survival, modulates guide axonal path finding, and participates in synaptic plasticity during development (*2*). On the other hand, galectin-1 enhances axonal regeneration in a lectin-independent way, an effect which involves activation of the DeltaFosB transcription factor (*17*). In addition, galectin-3 promotes nerve growth factor (NGF)-mediated neuronal differentiation through Ras/MAPK-dependent and -independent signaling pathways (*18*).

Hematopoietic System

All hematopoietic lineages are, to some extent, influenced by galectin signaling (Table 2). Proliferation and differentiation of hematopoietic stem cells are regulated by galectin-1 through a biphasic mechanism; Although low doses of galectin-1 favor the differentiation of erythroid and granulocyte-macrophage lineages, exposure of hematopoietic progenitors to high doses of this lectin abrogates such effects (*22*). Moreover, myeloid lineage differentiation is associated with dramatic changes in the expression of galectins-3, -9, and -10 (*23*).

Polymorphonuclear Neutrophils and Mast Cells. In general, galectins are key immunological mediators that are substantially upregulated at sites of inflammation. Mast cells from galectin-3-deficient mice are functionally defective as shown by diminished histamine release and reduced cutaneous anaphylactic reactions. Mechanistically, these effects are associated with lower levels of JNK1 activation (*24*). On the other hand, galectin-1 limits neutrophil recruitment to activated endothelium by decreasing the extent of neutrophil capture, rolling, and adhesion on activated EC monolayers (*26*). In addition, galectins-1 and -3 are instrumental in the regulation of neutrophil metabolism and functionality through activation of the superoxide-producing NADPH oxidase and stimulation of different neutrophil processes including the respiratory burst, degranulation and phagocytosis (*28, 29*). The activation of the p38 MAPK pathway appears to be, at least in part, critical for these effects (*29*). Finally, galectins -1 and -3 also regulate the neutrophil life-span by facilitating neutrophil phagocytosis by macrophages. This process, called "preaparesis," is mediated by phosphatydilserine exposure in leukocytes in the absence of a fully-executed cell death program, requires mobilization of cytosolic Ca^{2+} and entails action of the Src family of kinases and phospholipase Cγ (*30*). Remarkably, other galectins also participate in the regulation of neutrophil functionality; galectin-8 modulates neutrophil adhesion via interaction with integrin α_M/CD11b and the promatrix metalloproteinase-9 (*27*), whereas galectin-9 is a potent eosinophil chemoattractant and critical regulator of cell adhesion (*25*).

Monocytes/Macrophages. Galectin-1 has been shown to promote the alternative activation of macrophages by upregulating arginase activity, favoring the production of prostaglandin E_2 (PGE_2), and blunting expression of inducible nitric oxide synthase (iNOS) (*31*). Additionally, this glycan-binding protein controls FcγRI-mediated phagocytosis and MHC II-dependent antigen presentation through signaling via the ERK1/2 dependent pathway (*32*). Interestingly, galectin-3 also regulates alternative macrophage activation through crosslinking of CD98 and stimulation of phosphatidylinositol 3 kinase (PI3K)-dependent

Table 2
Galectin-mediated signaling pathways in hematopoietic tissues

Cell/Function	Galectin member	Signaling pathway	Refs
Stem cell proliferation	Galectin-1	?	(*22*)
Myeloid differentiation	Galectins-3, -9, -10	?	(*23*)
Mast cell function	Galectin-3	JNK-1	(*24*)
Eosinophil chemoattraction	Galectin-9	?	(*25*)
Neutrophil recruitment to endothelium and adhesion	Galectin-1, -8	?	(*26, 27*)
Neutrophil metabolism and	Galectins-1, -3	p38 MAPK,	(*28, 29*)
life-span	Galectins-1, -3	i[Ca^{2+}] mobilization, Src, PLCγ	(*30*)
Monocyte activation/	Galectin-1	PGE_2, iNOS,ERK1/2, p44/42 MAPK	(*31–33*)
Phagocytosis/Antigen presentation	Galectin-3	PI3K, G-proteins, NF-κB	(*34, 35*)
DC differentiation/activation	Galectin-3	?	(*36*)
	Galectin-9	Tim-3, p38, ERK1/2 MAPK	(*37*)
	Galectin-1	Syk, PKC, JAK2-STAT3	(*38–40*)
Thymocyte differentiation	Galectins-1, -3, -9	ERK, Bcl-2	(*41–43*)
T cell differentiation	Galectin-1	ERK	(*44*)
T cell recruitment to the endothelium	Galectin-1, -8	Pyk, ERK	(*45, 46*)
T cell microdomains formation	Galectin-1	CD45 phosphatase	(*47, 48*)
Early signaling events of T cell activation	Galectin-1	Lck, Nck, Wasp/F-actin	(*48*)
		inositol-1,4,5 triphosphate	(*1*)
		i[Ca^{2+}] mobilization, PLCγ1	
		ERK, p38MAPK, AP1, NFAT	(*49–51*)
	Galectin-3	Alix	(*52*)
	Galectin-1	TCRζ	(*53*)
Cell cycle arrest in T cells	Galectin-1	Upregulation IFNγRα/β	(*54*)
Induction of T cell apoptosis	Galectin-1	Upregulation IFNγRα/β	(*54*)
		Endonuclease G nuclear translocation	(*55*)
		Fas/Caspase 8-mediated	(*56, 57*)
		Bcl-2/Bax dysbalance, AP1, ERK	(*43, 50*)
	Galectin-2	Caspases 3/9, cytochrome *c*, altered Bcl-2/Bax ratio	(*58*)
	Galectin-9	Bcl-2, i[Ca^{2+}]$^{-}$calpain-caspase 1	(*43, 73*)
	Exo-Galectin-3	i[Ca^{2+}], citochrome *c*, caspase 3	(*59*)
T cell resistance to apoptosis	Endo-Galectin 3	Mitochondrial integrity, Bcl-2, annexins, caspase-8	(*60*)
Differentiation of T-cell effectors and regulators	Galectins-1, -9	Cytokines, GM1/TRPC5/i[Ca2+]	(*61–64*)
B-cell differentiation	Galectin-1	Integrin clustering	(*65*)
B-cell survival and differentiation	Galectins 1, -3	Blimp-1, Bcl-2	(*66–68*)
Platelet activation and function	Galectin-1	i[Ca^{2+}], cyclic nucleotides	(*69*)

signals (*34*). Galectin-3 is abundantly expressed by activated macrophages and influences phagocytosis and chemotaxis through G-protein-coupling signaling mechanisms (*35*). Likewise, galectin-1 stimulates monocyte chemotaxis via activation of the p44/42 MAPK pathway and a Pertussis toxin-sensitive mechanism (*33*). In addition, a direct link between galectin-3 expression, macrophage activation, and expression of the NF-κB transcription factor has clearly been demonstrated (*2*).

Dendritic Cells. Research over the past few years revealed the ability of individual members of the galectin family to control dendritic cell (DC) function by differentially modulating their capacity to orchestrate or terminate the immune response. Although not affecting DC differentiation or maturation, galectin-3 fine-tunes the immunostimulatory capacity of DCs (*36*). On the other hand, galectin-9 promotes DC maturation via interaction with the cell surface mucin-like protein Tim-3 and

signaling through the p38 and ERK1/2 MAPKs (*37*). Galectin-1 also plays a relevant role in controlling DC activation and migration through Syk and PKC signaling (*38, 39*). Remarkably, recent findings revealed that, in spite of their maturation and/or activation status, galectin-1-glycan interactions favor the generation of DCs with greatly enhanced tolerogenic potential *in vivo*. This inhibitory effect sets the basis for an immunoregulatory circuit propagated from DCs to T cells, which involves the secretion of IL-27 and IL-10 and activation of the JAK2-STAT3 signaling pathway (*40*).

T lymphocytes. T cells are certainly the best studied cellular model in which intracellular signaling pathways triggered by galectin–glycan lattices have been explored. Galectins can regulate the fate of T cells during their development in the thymus and following their emigration to peripheral tissues and secondary lymphoid organs (*1*). Endogenous galectin-1 contributes to shaping the T cell compartment by favoring negative selection through rapid and transient ERK activation (*41*). Furthermore, galectin-3 inhibits interactions between thymocytes and thymic epithelial cells and controls thymocyte migration and survival during T cell maturation (*42*). Likewise, galectin-9 expressed by thymic epithelial cells can control thymocyte survival through a Bcl-2-inhibitable mechanism (*43*).

Recent evidence indicates that galectin-1 controls TCR binding and ERK-dependent signals to regulate $CD8^+$ T cell expansion (*44*). In addition, this glycan-binding protein acts as a negative regulator of T-cell recruitment to the endothelium. Using siRNA to knockdown galectin-1 in endothelial cells, Norling et al. found that galectin-1 limits T-cell capture, rolling, and adhesion to activated endothelial cells under flow (*45*). T-cell adhesion to endothelium is also regulated by the interaction of galectin-8 with the α_4 integrin, which results in the phosphorylation of Pyk and ERK1/2 (*46*). Remarkably, galectins can bind to a wide range of cell surface glycoproteins and glycolipids (CD45, CD43, CD3, CD2, CD4, GM1, CTLA4, and CD7) and trigger distinct signaling pathways and cellular responses (*e.g.* apoptosis, receptor endocytosis, immune synapse formation) by forming geometrically-assembled multivalent interactions called "lattices" on the surface of T cells (*1, 47*). In the absence of TCR ligands, galectin–glycan lattices retain the highly glycosylated phosphatase CD45 in GM1-enriched microdomains concurrently blocking downstream signaling (*48*). During early steps of T-cell activation and synapse formation, sustained upregulation of galectins is observed, resulting in negative regulation of TCR signaling. *N*-glycans exposed on CD45 are modified with subsequent changes in lattice formation and relocalization of this phosphatase outside microdomains, allowing the binding of Lck/Zap-70 to CD3ε and subsequent recruitment of Nck/Wiscott Aldrich Syndrome protein (WASp) (*48*); these interactions induce F-actin microfilament rearrangements (*48*). Investigation of the signal transduction events involved in galectin-1-mediated T-cell signaling revealed early generation of inositol-1,4,5, triphosphate, tyrosine phosphorylation, phospholipase Cγ1 activation and increased influx of intracellular Ca^{2+} with transient release from internal stores (*1*). Furthermore, galectin-1 strongly modulates T cell signaling through the involvement of ERK-MAP kinase cascade, activation of $p56^{lck}$ and ZAP70-mediated tyrosine phosphorylation, and activation of AP-1 and NFAT transcription factors (*49–51*). Moreover, this endogenous lectin can also promote partial phosphorylation of the TCR-ζ chain and the generation of inhibitory pp21ζ, thus antagonizing TCR signal transduction processes (*53*). Interestingly, the phosphorylation pattern observed during TCR-mediated activation in the presence of galectin-1 is qualitatively different from that observed in the absence of this lectin (*53*), implying that galectins may regulate T-cell activation and function by imprinting qualitative changes in the "signalosome." In addition, recombinant galectin-1 inhibits cell cycle progression on activated T cells by inducing arrest in the G_2 and S phases and suppresses T cell proliferation and IL-2 production (*54*). Galectin-1 has been reported to trigger T-cell death through direct and indirect mechanisms involving modulation of a variety of downstream and upstream signaling pathways (*1*). An indirect mechanism has been provided by Allione et al. who reported galectin-1-induced upregulation of α and β chains of the IFN-γ- receptor on activated T lymphocytes, rendering these cells sensitive to IFN-γ-induced apoptosis (*54*). However, galectin-1 can also promote T-cell apoptosis through direct mechanisms involving segregation of glyco-receptors (CD45, CD43, CD2, and CD7) to membrane microdomains (*47*). However, the intracellular signals transduced by these complexes are still poorly understood. In some circumstances, galectin-1-induced T-cell death has been reported to proceed via a caspase-independent mechanism that involves rapid translocation of endonuclease G from the mitochondria to the nucleus. This process occurs in the absence of cytochrome c release or nuclear translocation of the apoptosis-inducing factor (AIF) and before the loss of mitochondrial membrane potential (*55*). However, under other circumstances, galectin-1 can sensitize a caspase- and cytochrome c-dependent apoptotic pathway that is blocked by a neutralizing anti-Fas monoclonal antibody (*56, 57*). Moreover, exposure to galectin-1 favors a disbalance in the Bcl-2/Bax ratio with a predominance of proapoptotic Bax and activation of ERK-1/2- and AP-1-dependent pathways (*50*). Thus, galectin-1 may trigger different apoptotic pathways to regulate T-cell death; an effect which may depend on the different concentrations used for *in vitro* assays, the use of T cell lines versus primary T cell cultures as targets cells and/or the different culture conditions (*e.g.* the use of dithiotreitol in cell culture). In this regard, other reports showed that galectin-1 does not promote apoptosis on T cells but instead is capable of modulating the synthesis and secretion of cytokines including IL-10 and IFN-γ (*30*).

In addition to galectin-1, galectin-2 also binds to T cells in a β-galactoside-specific manner and modulates survival of activated T cells. This effect involves binding to β_1 integrin and involves activation of caspases-3 and -9, cytochrome c release, disruption of the mitochondrial membrane potential, and

increase in the Bax/Bcl-2 ratio (*58*). Furthermore, recent studies showed that galectin-3 can negatively regulate TCR-mediated $CD4^+$ T cell activation at sites of immunological synapse through specific interaction with Alix, a protein implicated in protein transport and regulation of cell surface receptor expression (*52*). However, similar to galectins-1 and -2, this "chimera-type" galectin can also promote T-cell apoptosis and this effect involves cytochrome c release and caspase-3 activation (*59*). On the contrary, intracellular galectin-3 induces resistance to apoptosis by regulating mitochondrial integrity and reducing the production of reactive oxygen species (ROS) (*2, 60*). In fact, galectin-3 has been proposed to be a key molecule capable of integrating cellular choices among different apoptosis-regulatory pathways and facilitating the activation of caspase-8 and the death-inducing signaling complex (DISC) (*70*). Studies of subcellular protein shuttling indicated that galectin-3 translocates into the mitochondria when cells are exposed to apoptotic stimuli through a mechanism that involves binding to sinexin (*60*). Moreover, sequence analysis of galectin-3 revealed the presence of a four amino-acid anti-death-motif (Asp-Trp-Gly-Arg (NWGR)) that is highly conserved within the BH1 domain of the Bcl-2 protein. This motif appears to be essential for the carbohydrate-binding activity of galectin-3 (*71*). Although galectin-3 does not regulate the expression levels of individual members of the Bcl-2 family (Bcl-2, Bcl-xL, and Bax), this lectin is able to interact with Bcl-2 in a lactose-inhibitable fashion (*72*). This interaction may regulate Bcl-2 function including Bcl-2 downregulation induced by other galectins including galectin-1. Further studies are required to determine whether the proapoptotic or antiapoptotic activities of galectin-3 prevail *in vivo*. Furthermore, "tandem-repeat"-type galectins, including galectin-9, can also modulate T-cell viability. These proapoptotic effects can be blocked by intracellular Bcl-2 and involve distinct signaling pathways to those triggered by galectin-1 (*43*). Mechanistically, galectin-9-mediated apoptosis occurs via a Ca^{2+}–calpain–caspase-1 pathway (*73*).

Differentiation of individual T-cell subsets (including effector and regulatory T cells) is characterized by particular patterns of cellular glycosylation and modulation of the expression and function of endogenous galectins (*61, 62*). Recent findings showed that Th1 and Th17 cells share the repertoire of cell surface saccharides (*N*- and *O*-glycans) that are critical for galectin-1 binding and subsequent cell death, whereas Th2 cells are resistant to galectin-1-induced apoptosis through specific α2-6 sialylation of cell surface glycoproteins (*62*). This effect has been substantiated by findings in galectin-1-deficient mice that develop hyper-Th1 and Th17 responses following challenge with inflammatory stimuli (*62*). Consistent with those observations, recent studies showed that Th2 cells can control the survival of Th1 cells through a galectin-1-dependent mechanism (*63*). In addition, elegant studies showed that regulatory T cells overexpress galectin-1 that contributes to suppress effector T cell function through crosslinking of the ganglioside GM1 and further activation of the TRPC5 channel (*61, 64*). Collectively, these findings imply multifunctional roles of individual members of the galectin family in fine-tuning T-cell activation, differentiation and survival with critical implications at the crossroad of tolerance and inflammation.

B lymphocytes. Galectins-1 and -3 play key roles in B-cell physiology including B cell differentiation and tolerance (*1*). Bone marrow stromal cell-derived galectin-1 regulates B-cell differentiation through interactions with $\alpha_4\beta_1$ (VLA-4), $\alpha_5\beta_1$ (VLA-5), and $\alpha_4\beta_7$ integrins (*65*). These glycosylation-dependent interactions lead to pre-BCR relocalization into a synchronized synapse that requires actin polymerization (*74*). In the periphery, galectins-1 and -3 are markedly upregulated after B-cell activation (*66*). In addition, galectins-1 and -3 play important roles in B-cell survival and plasma cell differentiation through regulation of the Blimp-1 transcription factor (*66–68*).

Platelets. In addition to its ability to modulate lymphoid and myeloid cell compartments, galectin-1 can also regulate human platelet activation and function (*69*). This endogenous lectin synergizes with ADP or thrombin to induce platelet aggregation and ATP release. Furthermore, galectin-1 induces F-actin polymerization, upregulation of P-selectin, and GPIIIa expression, promotes shedding of microvesicles, and triggers conformational changes in GPIIb/IIIa. A mechanistic analysis revealed the involvement of Ca^{2+} and cyclic nucleotide-dependent pathways in galectin-1-mediated control of platelet activation (*69*).

GALECTINS IN TUMOR BIOLOGY

A brief representation of the signaling pathways triggered by galectins in the tumor microenvironment is shown in (Table 3). The processes of oncogenesis and metastasis are associated with a dramatic remodeling of cell surface glycans expressed by cancerous, stromal and immune cells in the tumor microenvironment (*1*). These alterations result from genetic or epigenetic changes in the activities of glycosyltransferases, glycosidases, or chaperons that promote a switch from a "normal" to an "altered" cell surface glycome (*1*). An example illustrating this concept is represented by the expression of the β1,6-*N*-acetylglucosaminyltransferase V (Mgat5) that is substantially increased during cellular transformation (*101*). These changes in glycan composition are associated with a prolonged half-life of cell surface receptors involved in cellular growth, endocytosis, and cytokine signaling (*102*). Mammary tumor cells from Mgat5-deficient mice, in which galectin–glycan lattices are prevented, display reduced sensitivity to cytokines (*102*), suggesting that lattices formed between galectins and *N*-glycans can control cell surface receptor expression, endocytosis, and signaling.

Tumor Cell Adhesion

Tumor cell adhesion to substrates is strongly dependent on integrin-mediated cellular signaling. Integrins, which participate in extracellular matrix (ECM)-cell interactions and cytoskeleton reorganization, exhibit several *N*-glycosylation sites that are

Table 3
Galectin-mediated signaling pathways involved in tumor biology

	Function	Galectin member	Signaling pathway	Refs.
Cell adhesion	Promotion of cell motility	Galectin-1	PKCε, GTPases	(*75, 76*)
	Promotion of adhesion	Galectin-3	Integrin, FAK, PI3K, F-actin	(*77*)
	Promotion of adhesion	c-Galectin 8	Integrins, FAK, paxillin, ERK, PI3K	(*78*)
	Inhibition of adhesion	s-Galectin 8	Akt, JNK, p21	(*79*)
Cell proliferation	Promotion of tumor cell proliferation	Galectin-1	H-RAS-GTP, Raf-1, MEK, ERK	(*80, 81*)
	Induction of G_2 arrest in tumors	Galectin-1	Ras, MEK, ERK, p27, p21	(*82, 83*)
	Proliferation of breast cancer cells	Galectin-3	K-Ras, ERK, cyclin D1 promoter	(*84, 85*)
	Inhibition of proliferation of prostate cancer cells	Galectin-3	Cyclin E, A, p21, p27, Rb Phosphorylation-dependent	(*86, 87*)
	Growth suppression in colon carcinoma	Galectin-7	?	(*88*)
	Growth arrest	Galectin-8	JNK, Akt, p21	(*79*)
	T lymphoma cell arrest	Galectin-9	Cyclins D1,D2, B1, Cdk1, Cdk4, Cdk6, Cdc25C, cMyc	(*89*)
	G_1 arrest in tumor cells	Galectin-12	?	(*90*)
Cell apoptosis	Resistence to chemotherapy	Galectin-1	HSP-70-mediated lysosomal permeabilization and cathepsin B release	(*91, 92*)
	Anti-apoptotic effect in J82 bladder cancer cells	Galectin-3	Akt activation	(*93*)
	Protection from breast cancer anoikis	Galectin-3	Akt dephosphorylation	(*94*)
	Induction of cellular apoptosis	Galectin-7	JNK, caspase 3, cytochrome c	(*14*)
Gene regulation	Transcription factor regulation	Galectin-1	AP-1	(*95*)
		Galectin-3	β-catenin, Axin, Tcf-4, NF-κB, c-Jun	(*96, 97*)
	Response to hypoxia	Galectin-3	?	(*98*)
	Regulation of hypoxia-related genes	Galectin-1	CTGF,ATF3,PPP1R15A,HSPA5, TRA1,CYR61, BEX2, OPR150	(*91, 99, 100*)

well-recognized targets of galectin binding (*2*). Galectin-1 regulates β_1-integrin cell surface expression and trafficking via PKCε/vimentin-mediated signaling (*75*). In addition, galectin-1 controls the reorganization of the actin cytoskeleton by regulating small GTPase activities (*76*). Both effects have an important impact on the migratory properties of glioma cells. On other hand, through interaction with the $\alpha_5\beta_1$ integrin, exogenous galectin-3 controls tumor cell adhesion and motility via FAK and PI3K activation and local F-actin reorganization (*77*). On the other hand, galectin-8 can bind to $\alpha_3\beta_1$ and $\alpha_6\beta_1$ integrins to modulate tumor cell adhesion (*103*). Interestingly, opposite effects of galectins on cell adhesion have been observed. When immobilized to substrate, galectin-8 promotes cell adhesion and cytoskeleton reorganization, including formation of F-actin-containing microspikes (*78*). These effects are mediated through tyrosine phosphorylation of FAK and paxillin, and activation of ERK and PI3K signaling cascades. These signaling complexes are much more robust and are of longer duration than those induced upon cell adhesion to fibronectin (*78*). However, when presented as a soluble molecule, galectin-8 negatively regulates cell–cell interactions and tumor growth. This effect is mediated by the activation of Akt and JNK pathways followed by upregulation of the p21 cell cycle inhibitor (*79*).

Cellular Transformation

Complex and paradoxical effects on tumor cell behavior have been assigned to galectin-1. In a glioblastoma model, this lectin was reported to act as a growth-promoting factor capable of sustaining tumor cell proliferation and a protecting factor mediating chemoresistance (*80, 91*). On the other hand, exogenous galectin-1 can also induce a G_2 cell cycle arrest and promote tumor cell apoptosis (*104*). One candidate intracellular ligand for galectin-1 with transforming and growth-regulatory activities is the oncogene H-Ras. Interaction between H-Ras and galectin-1 promotes activation of the Ras-Raf-MEK-ERK signaling pathway at the expense of PI3K (*81, 82*). Depending on the different conditions of galectin-1 expression and presen-

tation, this endogenous lectin can: (*a*) increase the levels of membrane-associated Ras, Ras-GTP and ERK, resulting in cellular proliferation (*80*) or (*b*) promote the transcriptional regulation of p27 and p21, an effect that results in inhibition of cyclin-dependent kinase 2 activity, G_1 cell cycle arrest, and tumor cell growth inhibition (*83*). On other hand, galectin-1 has been shown to mediate chemoresistance in melanoma and glioma tumor cells. Mathieu et al. found that galectin-1 downregulation increases tumor cell autophagy mainly through HSP-70 lysosomal membrane permeabilization and stress-mediated response (*92*). Hence, the effects of galectin-1 on cell cycle progression, proliferation, and cell death appear to be dependent on the target cell type, its concentrations at sites of tumor growth, or the relative abundance of the dimeric versus monomeric forms of the protein.

With regards to galectin-3, this protein is markedly upregulated when quiescent cells are stimulated by serum to enter the cell cycle (*105*), suggesting an active role of this lectin in the intrinsic control of cell fate decisions. Galectin-3 showed a positive role in the proliferation of human breast cancer MDA-MB-435 cells (*84*). However, and similarly to galectin-1, galectin-3 may also display dual effects, acting also as a negative regulator of cell cycle progression. For example, in human prostate cancer, galectin-3 expression decreases in association with the progression of the disease. Moreover, overexpression of galectin-3 in the prostate cancer cell line LNCaP resulted in reduced proliferation and decreased tumor formation when injected into nude mice (*86*). These apparently contrasting effects on the cell cycle have been explained by the differential subcellular compartmentalization of this protein. In fact, nuclear expression of galectin-3 is associated with cell cycle arrest, whereas cytoplasmic expression of this lectin is linked to tumor cell proliferation and cell cycle progression (*106*). The mechanisms responsible of galectin-3-mediated cell cycle regulation remain only partially understood. The intracellular signaling pathways triggered by galectin-3 when acting as a positive regulator of the cell cycle involve an increase in active K-Ras coupled with loss of N-Ras, whereby PI3K activity is blunted and shifted to the activation of ERK (*84*). Additionally, this effect involves the induction of cyclin D1 promoter activity through multiple cis-elements, including the SP1 and cAMP-responsive elements (*85*). On the other hand, phosphorylation of galectin-3 is required to cause G_1 arrest in the breast carcinoma BT549 cell line with concomitant protection against apoptosis induced by loss of cell anchorage (anoikis) (*107*). This effect is consistent with the observation that the phosphorylated form of galectin-3 is mostly present in quiescent cells (*87*). Noteworthy, galectin-3-mediated cell cycle arrest is also associated with upregulation of p21 with consequent hypophosphorylation of the retinoblastoma protein (*87*). Interestingly, galectin-3 displayed both anti- and proapoptotic activities against TNF-related apoptotic stimuli depending on the expressing cell type. Overexpression of galectin-3 in J82 human bladder carcinoma cells rendered these cells resistant to TRAIL-induced apoptosis, an effect that involved Akt signaling and activation (*93*). On the other hand, galectin-3-transfected BT549 human breast carcinoma cells were much more sensitive to TRAIL-induced apoptosis through a mechanism involving Akt dephosphorylation (*94*). The mechanisms leading to these apparently opposite effects of galectin-3 and their relationship with divergent signaling pathways are still uncertain. Based on the fact that galectin-3 exhibits a cell cycle-dependent expression and a restricted nuclear localization, it is possible to speculate that this endogenous lectin plays a tuning role in the control of cellular behavior; however, the molecular intermediates responsible of galectin-3 effects remain to be investigated.

Other galectin members also participate in cellular transformation and tumorigenesis (*3*). Galectin-7 gene (*Lgals7*) is an early transcriptional target of the tumor suppressor p53 (*14*). This galectin member suppresses *in vivo* growth of colon carcinoma cells (*88*) and induces apoptosis in different cell types (*12, 14*) by upregulation of JNK activity, caspase-3 activation, and cytochrome c release (*14*). On the other hand, galectin-8 induces growth arrest by promoting an increase in the cellular content of the cyclin-dependent kinase inhibitor p21, an effect that was preceded by an increase in JNK and Akt activities (*79*). Of note, the selection of JNK- or Akt-dependent pathways can switch the cellular outcome from apoptosis to growth arrest (*79*). Interestingly, it was found that a protease-resistant mutant of galectin-9 was capable of preventing the growth of adult T-cell leukemia (ATL) and lymphoma cells by promoting a cell cycle arrest. This effect leads to a reduction in the expression of cyclin D1, cyclin D2, cyclin B1, Cdk1, Cdk4, Cdk6, Cdc25C, and c-Myc (*89*). Also, galectin-12 has been identified as a negative regulator of cellular proliferation as overexpression of this "tandem-repeat" lectin in HeLa cells resulted in cell cycle arrest (*90*).

Control of Gene Expression

Several of the biological effects displayed by galectins in normal and pathological settings might be explained by direct regulation of gene expression. Starting from the late 1980s, it has been observed that galectins translocate from the cytoplasmic compartment to the nucleus, and copurification experiments have demonstrated their association with ribonucleoprotein complexes (*108*). Evidence of the relevance of intracellular galectins-1 and -3 as components of the pre-mRNA splicing machinery was clearly established as galectin-depleted nuclear extracts had markedly reduced splicing activity and abnormal spliceosome formation. Under these circumstances, reintroduction of recombinant galectins was sufficient to restore spliceosome activity (*108*). The precise molecular mechanisms underlying these functions are still under scrutiny. Yet, a direct interaction of galectins-1 and -3 with Gemin4 has been clearly demonstrated by pull-down experiments (*109*). Gemin4 forms complexes with SMN, Sm SnRNP and is implicated in pre-mRNA splicing. Of importance, and in contrast to previous assumptions, the galectin CRD appears to be necessary and sufficient

to modulate splicing activity (*108*). On the other hand, the N-terminal domain of galectin-3 acts as a dominant negative mutant by inhibiting splicing activity (*109*). A complete understanding of the nature and composition of this transcriptional complex as well as the co-factors required for their function and regulation will be critical to further analyze the intracellular functions of galectins and dissect the implicated signaling pathways.

Undoubtedly, galectins are key players of oncogenesis-associated deregulation of gene-expresion. Several transcription factors that play an important role in cellular growth and transformation are modulated by galectins. In this regard, an elegant study showed that galectin-3 binds to β-catenin and Axin, two regulators of Wnt signaling (*96*). Galectin-3-β-catenin complexes translocate to the nucleus where they become associated with Tcf-4, and this ternary complex controls the expression of cyclin D1 and c-Myc (*96*). Similarly, as demonstrated for peritoneal macrophages, galectin-3 expression in tumor cells is under the transcriptional control of NF-κB and c-Jun (*97*). In addition, galectin-3 promoter contains hypoxia-responsive elements and stimulates capillary tube formation of endothelial cells *in vitro* and angiogenesis *in vivo* (*98*). Finally, galectin-1 can also regulate angiogenesis through the control of several hypoxia-related genes. Particularly, oxygen-regulated protein 150 has been implicated in VEGF maturation (*99, 100*). Remarkably, AP-1-dependent expression of galectin-1 in classical Hodgkin lymphoma cells contributes to the establishment of tumor-immune privilege and tumor-immune escape by promoting the expansion of regulatory T cells and decreased survival of Th1 and $CD8^+$ T cells (*95*), suggesting that galectin-1 expression contributes to tumor cell evasion of immune responses. Thus, galectins can activate distinct signaling pathways in the tumor microenvironment to promote tumor cell transformation, proliferation, and survival and to regulate cell adhesion, migration, angiogenesis, and tumor-immune escape (*3*).

CONCLUDING REMARKS

Galectins can control diverse cellular processes including cell adhesion, differentiation, proliferation, and survival through intracellular or extracellular control of multiple signaling pathways. Each cell type integrates intrinsic and extrinsic signals to develop multiple functions that are activated or silenced in response to different galectins, which are localized either in the extracellular or intracellular compartments. The plasticity of a given cell type to respond to a wide variety of microenvironmental signals or to trigger distinct signaling pathways might probably explain why certain biological effects of galectins are cell-type specific. In addition, the ability of single members of the galectin family, with subtle or substantial variations in their saccharide specificity, to transduce distinct signaling events, might also provide a rational explanation for the functional divergences displayed by these multifunctional glycan-binding proteins. Thus, delineating and understanding galectin functions may not be as simple as it was originally predicted as the activity of individual galectins may rely on multiple factors including: (*a*) particular subcellular localizations; (*b*) ability to elicit protein-protein or protein-glycan interactions; (*c*) expression of candidate glyco-receptors on target cells; (*d*) the regulated activity of glycosyltransferases and glycosidases creating discrete "glycosylation signatures" on different cell types; (*e*) the conformational changes associated with the galectin-glycan complex; and (*f*) the nature and composition of the "signalosome" triggered by individual members of the family. Moreover, additional complexity is introduced by the occurrence of intracellular or extracellular modifications of galectins such as phosphorylation, oxidation, and cleavage (proteolysis), which may strongly influence their function in cellular signaling. In general, galectin-mediated signaling involves the sustained activation of mechanisms of membrane microdomain partition and regulation of upstream and downstream signaling molecules including activation or silencing of transcription factors (*e.g.* Wnt, NF-κB, Runt, AP-1, etc.), modulation of kinase-dependent pathways (*e.g.* MAPK, PI3K), and involvement of apoptosis and cell cycle regulators. Although the repertoire of signaling pathways triggered by different galectins may share some similarities, considerable differences may exist, as for example, galectin-3, but not galectin-1, has been found to use protein kinase C (PKC) and A (PKA) to induce MAPK activation, a common pathway implicated in galectin signaling (*110*). Although a large amount of information is currently available concerning the regulatory properties of galectins, the biological relevance of a relatively small family of highly conserved proteins exerting multiple biological tasks still remains to be explored. Under this puzzling scenario, critical questions need to be addressed regarding the extent of functional redundancy among different members of the galectin family *in vivo* and their specificity of action in simple or complex biological systems. Targeting individual galectins in particular cell types *in vivo* will be critical to understand subtle or substantial divergences in the biological functions of single members of the galectin family. Just as important is the examination of discrete signaling pathways triggered by individual members of the family to delineate the "galectin signalosome" and understand its biological relevance. Finally, the validation of galectins as new targets in biomedical therapy will require revising original experimental models to precisely define the cellular and molecular events associated with galectin signaling in each target cell and the relevance of these interactions in complete organisms.

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