ISSN 1349-9416 / CODEN GLYCAX

Aug 01, 2023

The multifaceted roles of galectins: glycan-binding proteins with multiple personalities

(Glycoforum. 2023 Vol.26 (4), A12) DOI: https://doi.org/10.32285/glycoforum.26A12

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Gabriel Rabinovich is Director of the Laboratory of Glycomedicine at the Institute of Biology and Experimental Medicine in Buenos Aires, Senior Investigator of the Argentinean National Research Council (CONICET) and Full Professor of Immunology at the University of Buenos Aires. His studies, documented in more than 320 publications in high profile journals demonstrated that **galectins can translate glycan-containing information into novel regulatory programs that control inflammation, suppress autoimmune pathology and allow cancer cells to evade immune responses. His findings opened new therapeutic possibilities in cancer and autoimmune diseases.** He has been distinguished as Member of the US National Academy of Science, European Molecular Biology

Organization and The World Academy of Science (TWAS), was recognized with several awards including the Karl Meyer (Society for Glycobiology), TWAS and Guggenheim Awards and received funding from the Mizutani Foundation for Glycoscience (Japan). Finally, Dr. Rabinovich delivered more than 450 lectures internationally, organized several scientific meetings and has done an extensive work in promoting glycosciences all over the world.

Multiple personality disorder is a psychiatric condition characterized by the spontaneous generation of alternate versions of self. The personalities have distinctive styles of expressing themselves, and they often possess separate names, living locations, and lifestyles. The transition from one personality to another is commonly triggered by environmental and interpersonal factors[1]. Unlike many cellular molecules and pathways, which are often specialized, this concept could be certainly applied to galectins, an evolutionarily conserved family of glycan-binding proteins with multifunctional roles in immunity[2]. These proteins often shuttle between different intracellular compartments (nucleus, cytoplasm, and organelles) and are released to the extracellular milieu, where they acquire different roles in response to diverse microenvironmental stimuli, including hypoxia, nutrient availability, intracellular and extracellular pH, cytokine milieu and the presence of proinflammatory or immunosuppressive signals. Within the immune system, galectins can elicit a wide array of important functions that tailor both innate and adaptive responses, playing key roles in shaping the choreography of immune cells in health and disease. Interestingly, the same galectin can function as a cytokine, chemokine, cell adhesion molecule, immune checkpoint molecule, danger-associated molecular pattern, or growth factor depending on different cellular programs, including activation, differentiation, and trafficking, or during pathologic conditions, such as pathogen invasion, autoimmune inflammation, fibrosis and cancer[3].

Since the discovery of the first galectin in 1975[4] and due to the large wealth of information reported on this lectin family, the definition of galectins has been constantly evolving. Their identity crisis started early after their discovery, given the multiple names they received based on diverse features, including their glycan-binding specificity, molecular

weights, or tissues and species of origin. Just to mention a few of them, these proteins were named as galaptins, electrolectin, S-type lectins, β-galactoside-binding lectins, C16, C34, Mac-2, or chicken lactose-lectin (CLL) until the term galectins was finally coined[5,6]. Accordingly, the term galectins is now generally accepted for those animal lectins that show affinity for β-galactosides and significant sequence similarities in the carbohydrate-binding site[7]. Although galectins were originally discovered in vertebrates, they are known to be widely distributed throughout the animal kingdom from sponge to mammals, and galectin-like domains have been also identified in viruses, and plants[8]. Whereas some members of the galectin family (e.g.,galectin-1 and -3) are widely expressed in a variety of cells and tissues either in a constitutive or inducible fashion, others have a more restricted localization, including galectin-4, 7, and -12, preferentially expressed in the gastrointestinal tract, skin, and adipose tissue respectively[9].

Regarding their glycan-binding specificities, galectins were originally defined as monogamous proteins that selectively bind to N-acetyllactosamine (LacNAc) terminal structures in both complex N-glycans and core-2 O-glycans. However, they appear to be more promiscuous than expected as significant differences in glycan-binding preferences have been identified, including recognition of sialylated, fucosylated, and even mannosylated structures[2,10], which may explain at least in part their different biological activities. Adding complexity to this picture, these glycans may be expressed in a myriad of cellular receptors, including receptor tyrosine kinases (e.g., VEGFR2), tyrosine phosphatases (e.g., CD45), mucins (e.g., CD43), integrins (e.g., β2-integrin), immune checkpoint receptors (e.g., Tim-3, PD-1, LAG-3) and antigen receptors (BCR and TCR complexes) present on the surface of immune cells. Thus, in contrast to the one protein-one receptor paradigm, in the case of galectins individual members of the family may co-opt a diverse set of glycoconjugates on the cell surface. Therefore, the functional response of cells to a given galectin may vary depending on the repertoire of potentially glycosylated ligands, generated by the coordinated action of glycosyltransferases and glycosidases and the engagement of a preferred set of cell surface receptors[2].

Galectins share all features of cytoplasmic proteins as they are not glycosylated themselves and have no signal peptide required for externalization through the conventional endoplasmic reticulum (ER)-Golgi pathway. However, these lectins are often secreted into extracellular spaces to exert a plethora of biological functions. Outside the cell, galectins can cross-link glycoconjugates located on the cell surface or in the extracellular matrix and trigger transmembrane signaling events leading to amplification or silencing of immune cell processes. How does the same galectin exert such different and often opposite effects? Although the mechanisms underlying the diverse functions of galectins are poorly understood, they likely depend on several factors, including the concentration reached in physiological or pathological microenvironments, their stability in oxidative versus reducing conditions, physicochemical properties (monomer/dimer equilibrium), cellular metabolic fluctuations, and the activation or differentiation status of particular target cells, leading to exposure or masking of specific glyco-epitopes[11]. Moreover, the multivalent nature of individual members of the galectin family, their biochemical and biophysical properties, and their cross-linking activity may determine distinct biological responses by inducing clustering, segregation, and endocytosis of a preferred repertoire of cell surface glycoconjugates[12].

One of the most widely studied functions of galectins relates to their cytokine-like activity. In fact, both galectins and cytokines share similar features as they are released in response to different stimuli (antigen challenge or stress) and act in an autocrine or paracrine fashion to promote or attenuate inflammatory responses. Like many cytokines, galectins can control immune cell activation, differentiation, expansion, and survival through fine-tuning a variety of signaling nodes[13]. In fact, recombinant as well as endogenous galectin-1 functions as a Th2-type cytokine in several models of autoimmune inflammation, including arthritis, uveitis, encephalomyelitis, and colitis[14-18], infection[19,20] and cancer[21,22]. The possible mechanisms underlying these effects may involve selective apoptosis of Th1 and Th17, but not Th2 cells through differential glycosylation of surface receptors[17] or selective regulation of TCR-driven signals on Th2 versus Th1 cells[23]. In this regard, a reciprocal cross-

regulation between galectins and cytokines has been documented in settings of inflammation and cancer. For example, galectin-1 consistently induces the synthesis of IL-10 and inhibits TNF-α and IFN-γ production[15,16,21,24 25], whereas galectin-3 is a strong inducer of TNF-α, IL-6, and IL-17[26–28]. Conversely, a variety of cytokines can control the expression of galectins, being pro-inflammatory cytokines such as TNF-α and IFN-γ strong inducers of galectin-3 and galectin-9 expression, whereas TGF-β and tolerogenic stimuli are potent promoters of galectin-1[29,30]. Thus, one of the most prominent personalities of galectins is represented by their ability to act as soluble cytokines and, by doing so, reprogramming innate and adaptive immune responses. In this regard, a key role shared by several members of the galectin family, including galectin-1, -3, -8, and -9, is their ability to promote the differentiation and stability of $CD4^+CD25^+FoxP3^+$ regulatory T cells[16,31–34].

Interestingly, and highlighting their alternative personalities, galectins also share some features with chemotactic and pro/anti-migratory factors as they can promote or inhibit the trafficking and recruitment of immune cells to sites of inflammation, infection, and tumor growth. Whereas galectin-3 enhances neutrophil motility and recruitment in response to bacteria, parasite, and fungi infections[35–37] and galectin-9 supports the transmigration of T cells through the extracellular matrix[38], galectin-1 inhibits the migration of neutrophils, T cells, and dendritic cells in a glycan-dependent fashion[39–42]. Interestingly, recent studies revealed that galectins can form hybrid heterocomplexes with chemokines, as demonstrated by interactions between galectin-3 and CXCL12[43]. This effect may result in inhibition or augmentation of their functional capacity[44,45]. Whether the marriage between galectins and chemokines is a selective or a promiscuous phenomenon and whether inflammation can sustain or interrupt these interactions via glycan-dependent mechanisms still remains an open question.

Moving forward to a third and sticky personality of galectins, these proteins can also behave as cell adhesion molecules (CAM) by positively or negatively regulating homotypic and heterotypic cell interactions. To illustrate this concept, galectin-3 can promote neutrophil adhesion and

extravasation through integrin-independent mechanisms in a model of *Streptococcus pneumoniae* infection[46]. On the other hand, galectin-1 inhibits T cell adhesion to extracellular matrix[25], and galectin-9 impairs T cell adhesion by blocking CD44-hyaluronan-dependent interactions[47]. Whether a network of different galectins may act in concert to modulate adhesiveness in pathophysiologically-relevant settings remains to be elucidated.

Yet, another emerging personality that galectins may co-opt relates to their ability to engage immune checkpoint receptors. Whereas galectin-3 can bind to cytotoxic T lymphocyte antigen-4 (CTLA-4) and lymphocyte activation gene-3 (LAG-3) and modulates the threshold of T cell activation[48,49], galectin-1 binds to CD45 modulating its phosphatase activity[17,50], and galectin-9 promotes T cell dysfunction through binding to both T cell immunoglobulin and mucin-domain containing-3 (TIM-3) and programmed death 1 (PD-1)[51]. Moreover, galectins themselves have been proposed to function as glyco-checkpoints that recalibrate the magnitude and nature of antitumor immune responses in different cancer settings[52]. Thus, galectins can shape the landscape of tumors by engaging a particular set of co-inhibitory receptors, highlighting their promising potential as targets in cancer immunotherapy. However, galectins are not only players in immunity, but also in other hallmarks of cancer, including angiogenesis, invasion, and proliferation, highlighting their multiple roles during tumorigenesis and metastasis[53].

Last but not least, other personalities have been attributed to galectins, by virtue of their capacity to recognize "self" or "non-self". These proteins have been shown to function as pattern-recognition receptors (PRRs) and danger-associated molecular patterns/ alarmins during host-pathogen interactions. In fact, upon infection, intracellular galectins (galectin-3, -8, and -9) can recognize glycan motifs expressed on disrupted membranes of damaged endosomes/lysosomes harboring bacteria, viruses or protozoa and send early alarm signalsto recruit various components of the autophagy machinery. Hence, galectins may orchestrate surveillance mechanisms that sense the integrity of endocytic vesicles, providing a unique form of intracellular antimicrobial defense and damage repair[54–56].

Moreover, galectin-1 has been also identified as an alarmin released as a consequence of cytosolic lipopolysaccharide sensing and subsequent induction of inflammatory cell death programs including pyroptosis and necroptosis[57]. Thus, galectins may serve as sensitive sensors of intracellular infections capable of re-wiring inflammatory responses, leading to pathogen eradication.

It has been proposed that the cause of 'Syndrome of Multiple Personalities' (also called 'Dissociative Identity Disorder') is likely a psychological response to interpersonal and environmental stresses[58]. Likewise, the different roles of galectins may be acquired, switched or abrogated in response to intracellular or extracellular stress, including inflammation, tumorigenesis, nutrient deprivation, and hypoxia. In conclusion, galectins are multitasking proteins which have evolved to fulfill several intracellular and extracellular functions in a glycan-dependent or independent fashion. Their ability to interpret the 'sugar code' of glycoconjugates, their abundance in cells and tissues, and their capacity to generate multivalent interactions with cognate receptors even in the absence of canonical ligands and to convey this structural information into biologically relevant responses[3,59], make these proteins unique in a highly specialized molecular universe. Definitely, the molecular bases underlying the multiple personalities of this complex and fascinating protein family are still a mystery and will be an important subject of investigation in the up-coming years, because after all… We all love mysteries.

Legend to Figure 1. The multiple personalities of galectins.
Within the immune system, galectins can elicit a wide array of important functions that tailor both innate and adaptive responses, playing key roles in shaping the choreography of immune cells in health and disease. Interestingly, the same galectin can function as a cytokine, pro-migratory factor, cell adhesion molecule, immune checkpoint ligand, pattern-recognition receptor or alarmin depending on different cellular programs, including activation, differentiation and trafficking, and pathologic conditions, such as pathogen invasion, autoimmune inflammation, fibrosis, and cancer.

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