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Do galectins serve as soluble ligands for immune checkpoint receptors?

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ABSTRACT

Hardly any set of molecules have been studied more extensively in immuno-oncology than immune checkpoint receptors and their ligands. However, with intense research both in experimental models and clinical settings, additional immune evasion mechanisms and immunosuppressive pathways are continuously being discovered. These include galectins, a family of soluble glycan-binding proteins that shape the nature and magnitude of antitumor immune responses by reprogramming the fate and function of lymphoid and myeloid cells. Extracellularly, they interact with a variety of glycosylated receptors, modulating their cell surface retention, endocytosis, segregation, and signaling. Remarkably, a growing body of evidence suggests that galectins can bind to immune checkpoint receptors, including the T cell immunoglobulin domain and mucin domain-3 (TIM-3), programmed death-1 (PD-1), lymphocyte activating gene-3 (LAG-3), cytotoxic T lymphocyte antigen-4 (CTLA-4) and the leukocyte Ig-like receptor subfamily B3 (LILRB3) and B4 (LILRB4), favoring their signaling activity and inhibitory function. However, more work is needed to dissect the precise mechanisms underlying these effects, particularly the interplay between galectins and canonical immune checkpoint ligands as well as the biochemical nature and glycan-binding dependence of these interactions. A better understanding of 'galectin-immune checkpoint' hubs will contribute to design novel immunotherapeutic modalities aimed at targeting galectin-driven circuits in a wide range of cancer settings.

INTRODUCTION

Galectins are a family of soluble glycan-binding proteins containing one or two highly conserved carbohydrate recognition domains (CRDs) that preferentially bind to lactosamine (LacNac; Galβ1-4NAcGlc) structures present on different cell surface receptors and the extracellular matrix.[1] Unlike other lectins such as C-type lectin receptors and sialic acid-binding immunoglobulin-type lectins (Siglecs), which are mostly transmembrane proteins,[2] galectins are synthesized as cytosolic proteins, reside in the cytosol or nucleus for much of their lifetime, and are released into the extracellular medium through non-classical secretory mechanisms bypassing the endoplasmic reticulum (ER)-Golgi system. This externalization pathway may include accumulation inside extracellular vesicles and activation of inflammatory cell death pathways, including pyroptosis and necroptosis.[3–6]

Galectins have been classified into three groups according to their structure: (a) the 'prototype' galectins (galectin-1, galectin-2, galectin-7 to galectin-10, galectin-13 and galectin-14), which contain a single CRD that may associate to form homodimers; (b) the 'tandem-repeat' galectins (galectin-4, galectin-8, galectin-9 and galectin-12), in which two CRDs occur within a single polypeptide chain connected by a short linker peptide and (c) the 'chimera-type' galectin-3, containing a single CRD and a large amino-terminal domain that contributes to oligomerization. In the past years, galectins have been proposed to play central roles in different hallmarks of cancer.[7] Particularly, they have emerged as key regulators of antitumor immune responses and novel targets of immunotherapy by shaping the fate and function of both lymphoid and myeloid cells.[8 9] Interestingly, expression of different galectins is altered on different cell types of the tumor microenvironment, particularly, tumor cells and their associated endothelium, stromal fibroblasts, and immune cells.[3] At the molecular level, they bind to a preferential set of glycosylated receptors, including the T cell receptor (TCR), the B cell receptor (BCR), integrins, cytokine receptors, tyrosine phosphatase receptors (eg, CD45) and tyrosine kinase receptors (eg, VEGFR2), forming multivalent lectin-glycan complexes, often termed lattices, that control receptor segregation, endocytosis, signaling and activation.[10] Moreover, emerging evidence suggests a possible role of galectins as functional ligands of different immune checkpoint receptors present on lymphoid and myeloid cells (figure 1).

To illustrate this concept, galectin-9 has been demonstrated to play a key role in immune

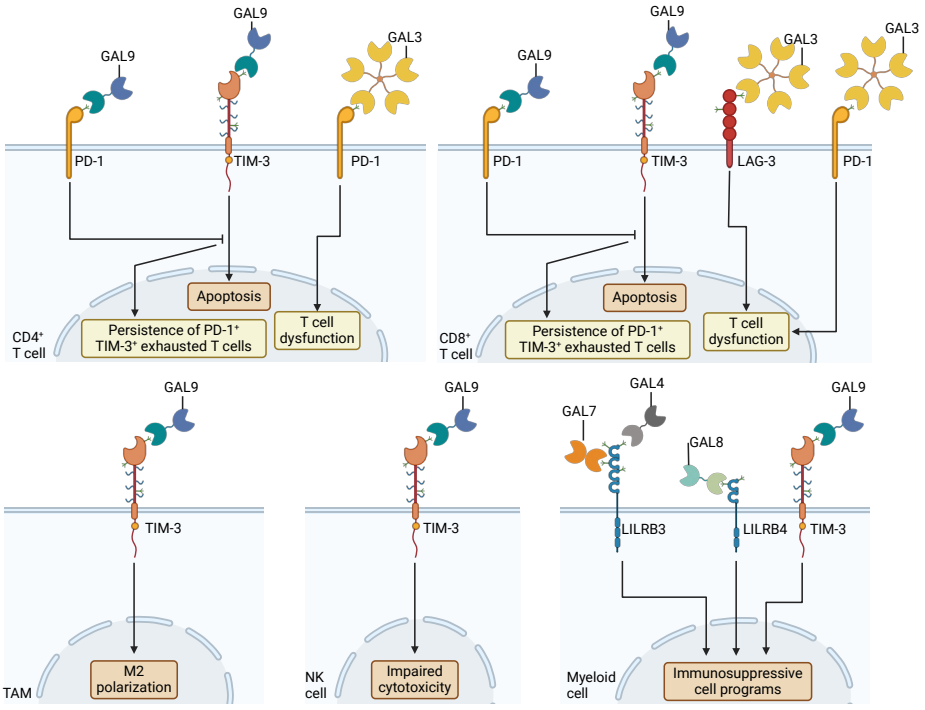

Figure 1 Galectins can bind to immune checkpoint receptors and trigger inhibitory pathways. Galectins can reprogram antitumor immune responses by shaping both lymphoid and myeloid compartments. Among the different inhibitory pathways triggered by these β-galactoside-binding proteins, a growing body of experimental evidence suggests that they can bind to a set of distinct immune checkpoint receptors including TIM-3, LAG-3, PD-1, LILRB3 and LILRB4, thus amplifying immune inhibitory circuits and facilitating tumor-immune escape in different cancer types. GAL: galectin; TAM: tumor-associated macrophages. Created with BioRender.com.

escape through mechanisms that are, at least in part, dependent on T cell immunoglobulin domain and mucin domain-3 (TIM-3) engagement.[11] Seminal work demonstrated that galectin-9 blunts T helper (Th)1 responses through binding to TIM-3.[12] Since then, the relevance of the TIM-3/galectin-9 axis in immuno-oncology has been studied in several tumor types, including solid tumors and hematological malignancies.[13–19] This pathway is implicated in critical inhibitory mechanisms that limit the magnitude of anticancer responses including induction of T-cell apoptosis, promotion of myeloid-derived suppressor cells (MDSCs) and inhibition of NK cell activity.[11] Supporting this notion, galectin-9 impaired NK cell-mediated cytotoxicity through association with TIM-3 in acute myeloid leukemia[20] and contributed to the expansion of $CD11b^{+}Ly\text{-}6G^{+}$MDSCs, thus favoring immune escape.[19] Interestingly, the human leukocyte antigen B (HLA-B)-associated transcript 3 (BAT-3) has been shown to counteract the TIM-3/galectin-9 axis by repressing the function of TIM-3 and protecting Th1 cells from galectin-9-mediated cell death.[21] However, evidence has also been raised highlighting the importance of TIM-3-independent immunoregulatory programs mediated by galectin-9.[22] In this regard, more recent evidence demonstrated that galectin-9 can also interact with the programmed death-1 (PD-1) pathway through N-glycan-dependent mechanisms, forming lattices that inhibit TIM-3-mediated apoptosis and promote persistence of $PD\text{-}1^{+}TIM\text{-}3^{+}$ T cells.[16 19] Notably, galectin-9/PD-1 interaction could not be interrupted by clinically available PD-1/PD-L1-blocking antibodies, suggesting different binding sites for this lectin on the PD-1 receptor.[16] Moreover, soluble V-domain Ig-containing suppressor of T cell activation (VISTA) synthesized by acute myeloid leukemia cells has been also shown to bind galectin-9 and enhance its immunosuppressive activity by creating a multiprotein barrier which prevents granzyme B release from cytotoxic T cells.[19]

However, galectin-9 may also bind to the T-cell costimulatory receptor 4-1BB (CD137), a member of the tumor necrosis factor receptor superfamily, in a site distinct from its natural ligand 4-1BBL, facilitating 4-1BB aggregation, signaling, and functional activity.[23] Interestingly, this tandem-repeat lectin may also promote immunosuppression in pancreatic adenocarcinoma through binding to Dectin-1, a C-type lectin receptor commonly upregulated in tumor-associated macrophages, highlighting the ability of this lectin to modulate both innate and adaptive antitumor responses.[24] In this regard, activation of the galectin-9/TIM-3 axis can drive M2 macrophage polarization leading to poor outcome in glioma patients.[14] Computational modeling and structural studies revealed the selective contribution of N- and C-terminal CRDs of galectin-9 to modulation of innate and adaptive immune functions.[25]

In spite of its paradoxical proinflammatory and anti-inflammatory activities in different pathophysiologic settings, galectin-3 has been shown to thwart antitumor responses in different cancer settings by inducing T-cell anergy, promoting T-cell apoptosis and favoring T cell exclusion through interruption of IFN-γ-driven chemokine gradients required for T cell infiltration.[26–28] In a model of triple negative breast cancer, tumor-secreted galectin-3 and a galectin-3-binding-protein have been shown to form a complex which interacts with CD45 receptor on T cells and induce expansion of regulatory T cells.[29] Interestingly, in a model of pancreatic ductal adenocarcinoma, galectin-3 has been shown to promote $CD8^+$ T-cell dysfunction through binding to the lymphocyte-activation gene 3 (LAG-3).[30] Accordingly, blockade of the galectin-3/LAG-3 axis has been validated in T cells from multiple myeloma patients.[31] However, the association of galectin-3 with other immune checkpoint pathways has not been studied in such detail. Wu *et al* reported increased levels of circulating anti-galectin-3 antibodies which correlated with superior clinical outcomes in patients with advanced melanoma receiving a combination of anti-CTLA-4 (ipilimumab) and anti-VEGF (bevacizumab) mAb,[32] suggesting a possible cross-talk between galectin-3 and the CTLA-4 pathway. In this regard, it has been demonstrated that CTLA-4 endocytosis and inhibitory signaling are highly dependent on elongation of complex branched N-glycans and the formation of galectin-N-glycan lattices.[33] Interestingly, ongoing clinical trials are conducted using galectin-3 inhibitors to improve anti-PD-1 therapy in metastatic melanoma and head and neck squamous cell carcinoma.[9 34] In this regard, the functional relevance of PD-1 glycosylation and a direct interaction between PD-1 and galectin-3 have recently been demonstrated.[35 36] These results highlight the importance of galectin-3 as an emerging target of cancer immunotherapy either alone or in different combination modalities.[34–37]

Like galectin-3 and galectin-9, galectin-1 has been shown to shape antitumor immune responses and foster immunosuppressive networks through modulation of lymphoid and myeloid cells.[3] These effects include induction of apoptosis of Th1, Th17 and $CD8^+$ T cells, expansion of $CD4^+$ and $CD8^+$ regulatory T cells and promotion of tolerogenic dendritic cells and immunosuppressive tumor-associated macrophages.[38–44] Several glycosylated receptors have been shown to mediate the functional activity of this lectin, including CD45, CD7, CD43, CD146, and VEGFR2.[1 26 39 40 42 45] Although the association of galectin-1 with immune checkpoint pathways remains elusive, this lectin has been shown to contribute to T-cell exclusion and resistance to PD-1 blockade.[46 47] Interestingly, similar to galectin-3, a strong antibody response to galectin-1 has also been observed in patients with metastatic melanoma responding to anti-CTLA-4 plus anti-VEGF therapy,[48] suggesting a possible interplay between galectin-1 and these pathways. In fact, we found that galectin-1 delineates resistance to anti-VEGF therapies, both in animal models and clinical settings.[42 49]

Finally, recent findings identified the leukocyte immunoglobulin-like receptor subfamily B3 (LILRB3) and the leukocyte immunoglobulin-like receptor subfamily B4 (LILRB4) as novel immune checkpoint receptors containing tyrosine-based inhibitory motifs (ITIMs) and preferentially expressed on myeloid cells.[50 51] Interestingly, galectin-4 and galectin-7 were discovered as high-affinity functional ligands of LILRB3, whereas galectin-8 has been demonstrated to bind LILRB4, triggering signaling of these receptors and regulating immunosuppressive myeloid cell programs[52 53]

In conclusion, given the broad immunoregulatory activities of galectins in secondary lymphoid organs and tumor microenvironments, it is becoming increasingly apparent that immune checkpoint receptors could mediate at least part of their functions (figure 1). However, in spite of considerable progress, it still needs to be explored whether these proteins operate independently of canonical immune checkpoint ligands and whether they act in a coordinated fashion to control the dynamics and signaling of these receptors. Meanwhile, several experimental and clinical studies are underway to evaluate the effects of galectin-targeted therapies using small molecule glycan inhibitors, natural polysaccharides, peptidomimetics, and neutralizing monoclonal antibodies, as standalone monotherapy or in combination with other anticancer treatments, including immune checkpoint blockers.[9]

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