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Galectins: emerging regulatory checkpoints linking tumor immunity and angiogenesis

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Immune checkpoints, a plethora of inhibitory pathways aimed at maintaining immune cell homeostasis, may be co-opted by cancer cells to evade immune destruction. Therapies targeting immune checkpoints have reached a momentum yielding significant clinical benefits in patients with various malignancies by unleashing anti-tumor immunity. Galectins, a family of glycan-binding proteins, have emerged as novel regulatory checkpoints that promote immune evasive programs by inducing T-cell exhaustion, limiting T-cell survival, favoring expansion of regulatory T cells, de-activating natural killer cells and polarizing myeloid cells toward an immunosuppressive phenotype. Concomitantly, galectins can trigger vascular signaling programs, serving as bifunctional messengers that couple tumor immunity and angiogenesis. Thus, targeting galectin–glycan interactions may halt tumor progression by simultaneously augmenting antitumor immunity and suppressing aberrant angiogenesis.

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Galectins as emerging immune checkpoints in cancer

The immune system is equipped with effective weapons to battle against cancer cells, but it is held in check by a number of inhibitory co-receptors including programmed cell death-protein-1 (PD-1) and cytotoxic T lymphocyte–associated antigen-4 (CTLA-4). These regulatory checkpoint pathways which promote immunological homeostasis and safeguard against the detrimental effects of exuberant inflammation can be co-opted by cancer cells to evade immune destruction [1]. Engagement of PD-1 or CTLA-4 by their specific ligands (PD-L1/PD-L2 or CD80/CD86 respectively) results in recruitment of Src homology 2-containing tyrosine phosphatase-2 (SHP2) or protein phosphatase-2A (PP2A), effects that ultimately lead to T-cell exhaustion [1]. Monoclonal antibody (mAb)-based therapies targeting CTLA-4 and/or PD-1/PD-L1 pathways have yielded significant clinical benefits, including durable cancer regression and increased overall survival in patients with various malignancies by unleashing anti-tumor immunity [2]. However, whereas significant clinical responses have been achieved in several patients, others show intrinsic resistance or maintain only short-term benefit as their tumors develop compensatory inhibitory pathways [2]. These include, among others, the lymphocyte activation gene-3 (LAG-3) and the T-cell immunoglobulin and mucin protein-3 (TIM-3) [3]. These co-inhibitory receptors, may act autonomously to control distinct aspects of antitumor immunity, suggesting that combinatorial strategies blocking distinct immune checkpoints may pave the way for successful cancer immunotherapy [2].

Galectins, a family of endogenous glycan-binding proteins, influence a variety of immune cell processes through intracellular or extracellular mechanisms [4]. These lectins can orchestrate immunosuppressive circuits by co-opting selected inhibitory receptors, disrupting co-stimulatory pathways and/or controlling activation, differentiation, and survival of immune cells [4]. According to their structure, galectins are classified into three different families: (a) 'proto-type' galectins (galectin-1, 2, 5, 7, 10, 11, 13, 14 and 15) which display one carbohydrate recognition domain (CRD) that can dimerize; (b) 'tandem-repeat' galectins (galectin-4, 6, 8, 9 and 12) which contain two homologous CRDs in tandem; and (c) the chimera-type galectin-3 which uniquely displays a CRD connected to a non-lectin N-terminal region responsible for oligomerization [5]. In spite of lacking the typical signal sequence required for classical secretion, most galectins are externalized through an unconventional route which precise mechanisms remain uncertain [4].

Galectins were originally discovered by their capacity to bind glyco-conjugates bearing the *N*-acetyl-lactosamine [Galβ(1–4)-GlcNAc; LacNAc] disaccharide; however compelling evidence indicates substantial differences

in glycan-binding specificities of individual members of the galectin family (including preferences for core 2-*O*-glycans, complex branched *N*-glycans or sialylated structures), which might explain differences in their biological activities [4,6,7]. Although these saccharide structures are widely distributed in a range of glycoconjugates, individual galectins may co-opt a particular set of glycosylated receptors, thus emphasizing the importance of protein–protein interactions and glycan density in dictating galectin-receptor preferences [6]. To illustrate this concept, galectin-3 preferentially binds to the T-cell receptor (TCR), CTLA-4, LAG-3, CD71 and CD45 [8,9••,10], whereas galectin-1 interacts with CD45, CD43, CD69 and the pre-B cell receptor (pre-BCR) [10–13] and galectin-9 co-opts TIM-3 and CD44 [14,15••]. Interestingly, some of these receptors including CTLA-4, LAG-3 and TIM-3 have been widely recognized as immune checkpoint molecules capable of de-activating immune cells [2]. Formation of multivalent galectin–glycan complexes contribute to assembly and organization of these receptors, controlling their segregation, internalization and signaling [4,6]. Hence, galectins may twist the fate of immune cells by controlling the stimulatory or inhibitory function of relevant glycosylated receptors.

Interestingly, whereas some galectins are broadly expressed, others are preferentially localized in certain tissues, including galectin-7 in the skin, galectin-12 in adipose tissue and galectin-4 in the gastrointestinal tract [6]. Particularly, galectin-1 is prominent in tolerogenic DCs [16–18] and $CD4^+CD25^+$ Tregs [19]. Furthermore, several tumors (including melanoma, Hodgkin's lymphoma, lung adenocarcinoma, breast adenocarcinoma, neuroblastoma, glioblastoma, ovary carcinoma, T-cell lymphoma and pancreatic adenocarcinoma) foster immune evasive programs through mechanisms involving galectin-1 [20–23,24•,25–27,28•,29,30••], galectin-3 [31,32••] and galectin-9 [33]. These galectin-driven regulatory circuits may also control formation of aberrant vascular networks [24,34–37], suggesting a galectin-mediated cross-talk between immune and vascular circuits in the tumor microenvironment (TME). In this review we discuss the relevance of galectin–glycan interactions as emerging regulatory checkpoints that control antitumor responses and link immunosuppression to angiogenesis.

Controlling T-cell fate and function

It has become increasingly clear that galectins play key roles in shaping T-cell biology by influencing T-cell activation, signaling and survival [6]. Galectin-1 antagonizes TCR-transmitted signals promoting contraction of the CD8T cell compartment [38]. Moreover, galectin-3 prevents TCR, CD4 and Lck clustering into GM1-enriched membrane microdomains, thereby adjusting T-cell signaling threshold through *N*-glycan-dependent mechanisms [39,40]. In addition, galectin-3 favors T-cell anergy of human tumor-infiltrating lymphocytes (TILs) by distancing the TCR from CD8 molecules [41]. More recently, Petit et al. added mechanistic insights to this picture showing that galectin-3 limits the formation of a functional secretory synapse in CD8 TILs by preventing optimal lymphocyte-function-associated antigen-1 (LFA-1) triggering and reducing adhesion to target cells [32••]. Moreover, galectin-3 destabilizes the immunologycal synapse by promoting TCR downmodulation through intracellular mechanisms involving interactions with Alix, an adaptor endocytic protein [42].

Interestingly, galectins also play direct inhibitory roles by engaging relevant glycosylated receptors, preventing their endocytosis and promoting their retention on the cell surface. In this regard, galectin-3-*N*-glycan complexes trap CTLA-4 on the surface of T cells and prolong inhibitory signals triggered by this immune checkpoint receptor [8]. Moreover, galectin-3 dampens antitumor responses through interactions with LAG-3 on the surface of CD8T cells, whereas galectin-9 binds to TIM-3 leading to T-cell exhaustion [9••,14], an effect that is counteracted by human leukocyte antigen B (HLA-B)-associated transcript 3 (Bat3) [43].

Galectin–glycan interactions may also control T-cell viability. Galectin-1 triggers T-cell apoptosis through binding to *N*-glycans and *O*-glycans on CD45, CD43 and CD7 or by sensitizing resting T cells to Fas-induced death [10,44]. Interestingly, galectin-1 selectively eliminates Th1-differentiated and Th17-differentiated cells as they express the repertoire of glycans required for galectin-1 binding; in contrast Th2 cells are protected from galectin-1-induced death via α2,6 sialylation of surface glycoproteins [45]. Likewise, galectin-9 deletes Th1, Th17 and CD8T cells through glycosylation-dependent binding to TIM-3 [14,46,47], while it augments secretion of T-cell-derived pro-inflammatory cytokines through TIM-3-independent pathways [48]. Interestingly, intracellular galectin-1 can sensitize T cells to apoptosis induced by extracellular galectin-1 [49], suggesting that inhibition of intracellular or extracellular galectin-1 may contribute to augment T-cell responses. In contrast, intracellular galectin-3 protects T cells from extracellular apoptotic stimuli [50], whereas, extracellular galectin-3 directly kills activated T cells [10]. Finally, galectins may also control T-cell differentiation, as galectin-1 and -9 interrupt generation of Th17 effector cells through mechanisms involving CD69 [12] or TIM-3 [46]. Thus, galectins limit effector antitumor T-cell responses through modulation of activation, differentiation, signaling and survival (Figure 1).

Fine-tuning the Treg compartment

Immune checkpoint pathways favor immune evasion programs not only by promoting exhaustion of effector T cells, but also by shaping the Treg compartment [2].

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