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REVIEW

Sweetening the hallmarks of cancer: Galectins as multifunctional mediators of tumor progression

María Romina Girotti[1]*, Mariana Salatino[2]*, Tomás Dalotto-Moreno[2], and Gabriel A. Rabinovich[2,3]

Hanahan and Weinberg have proposed 10 organizing principles that enable growth and metastatic dissemination of cancer cells. These distinctive and complementary capabilities, defined as the "hallmarks of cancer," include the ability of tumor cells and their microenvironment to sustain proliferative signaling, evade growth suppressors, resist cell death, promote replicative immortality, induce angiogenesis, support invasion and metastasis, reprogram energy metabolism, induce genomic instability and inflammation, and trigger evasion of immune responses. These common features are hierarchically regulated through different mechanisms, including those involving glycosylation-dependent programs that influence the biological and clinical impact of each hallmark. Galectins, an evolutionarily conserved family of glycan-binding proteins, have broad influence in tumor progression by rewiring intracellular and extracellular circuits either in cancer or stromal cells, including immune cells, endothelial cells, and fibroblasts. In this review, we dissect the role of galectins in shaping cellular circuitries governing each hallmark of tumors, illustrating relevant examples and highlighting novel opportunities for treating human cancer.

Introduction

The hallmarks of cancer, first introduced in 2000 and later updated in 2011 (Hanahan and Weinberg, 2000; 2011), have proved seminal in our understanding of cancer's common traits, aiding in rational drug development and combinations to treat cancer. Each hallmark constitutes a well-established process that a normal cell should undergo to enable tumor growth, survival, invasion, and metastasis. They represent a broad range of features regulated by a plethora of genetic, epigenetic, and posttranslational modifications, including phosphorylation, sumoylation, and glycosylation, which together contribute to tumorigenesis and tumor progression (Hanahan and Weinberg, 2011).

In the postgenomic era, a major paradigm shift emerged involving the identification of relevant glycosylation changes occurring during tumor progression (Pinho and Reis, 2015). These involve modifications in terminal sialylation, fucosylation, O-glycan truncation, and N- and O-linked glycan branching (Cagnoni et al., 2016). These changes have provided unique signatures that are being capitalized for the discovery of clinical biomarkers and the design of new therapeutic strategies. The information encrypted by the glycome is deciphered by different families of glycan-binding proteins or lectins, including sialic acid–binding Ig-like lectins (siglecs), C-type lectin receptors, and galectins (Rabinovich and Toscano, 2009). Among them, galectins gained considerable interest, given both their various roles in cancer progression and their prognostic and therapeutic implications (Liu and Rabinovich, 2005). Recently, galectins have attracted particular attention as tumor and stromal cells express large amounts of these proteins, which control the magnitude and nature of antitumor responses by sensing glycosylation changes in immune cells (Méndez-Huergo et al., 2017). Based on their structure, galectins are classified into three different families: (a) "prototype" galectins (Gal1, Gal2, Gal5, Gal7, Gal10, Gal11, Gal13, Gal14, and Gal15), which display one carbohydrate-recognition domain (CRD) that can dimerize; (b) "tandem-repeat" galectins (Gal4, Gal6, Gal8, Gal9, and Gal12), which contain two homologous CRDs in tandem; and (c) the chimera-type Gal3, which uniquely displays a CRD connected to a nonlectin N-terminal region responsible for oligomerization (Méndez-Huergo et al., 2017). This review discusses the role of galectins as "on-and-off" switchers of different hallmarks of cancer, illustrating relevant examples of their contribution to tumor progression (Fig. 1).

Sustaining proliferative signaling

A distinctive feature of cancer cells is their ability to maintain uncontrolled cell proliferation (Hanahan and Weinberg, 2011).

[1]Laboratorio de Inmuno-Oncología Traslacional, Instituto de Biología y Medicina Experimental, Consejo Nacional de Investigaciones Científicas y Técnicas, Buenos Aires, Argentina; [2]Laboratorio de Inmunopatología, Instituto de Biología y Medicina Experimental, Consejo Nacional de Investigaciones Científicas y Técnicas, Buenos Aires, Argentina; [3]Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, Argentina.

*M.R. Girotti and M. Salatino contributed equally to this paper; Correspondence to Gabriel A. Rabinovich: gabriel.r@ibyme.conicet.gov.ar.

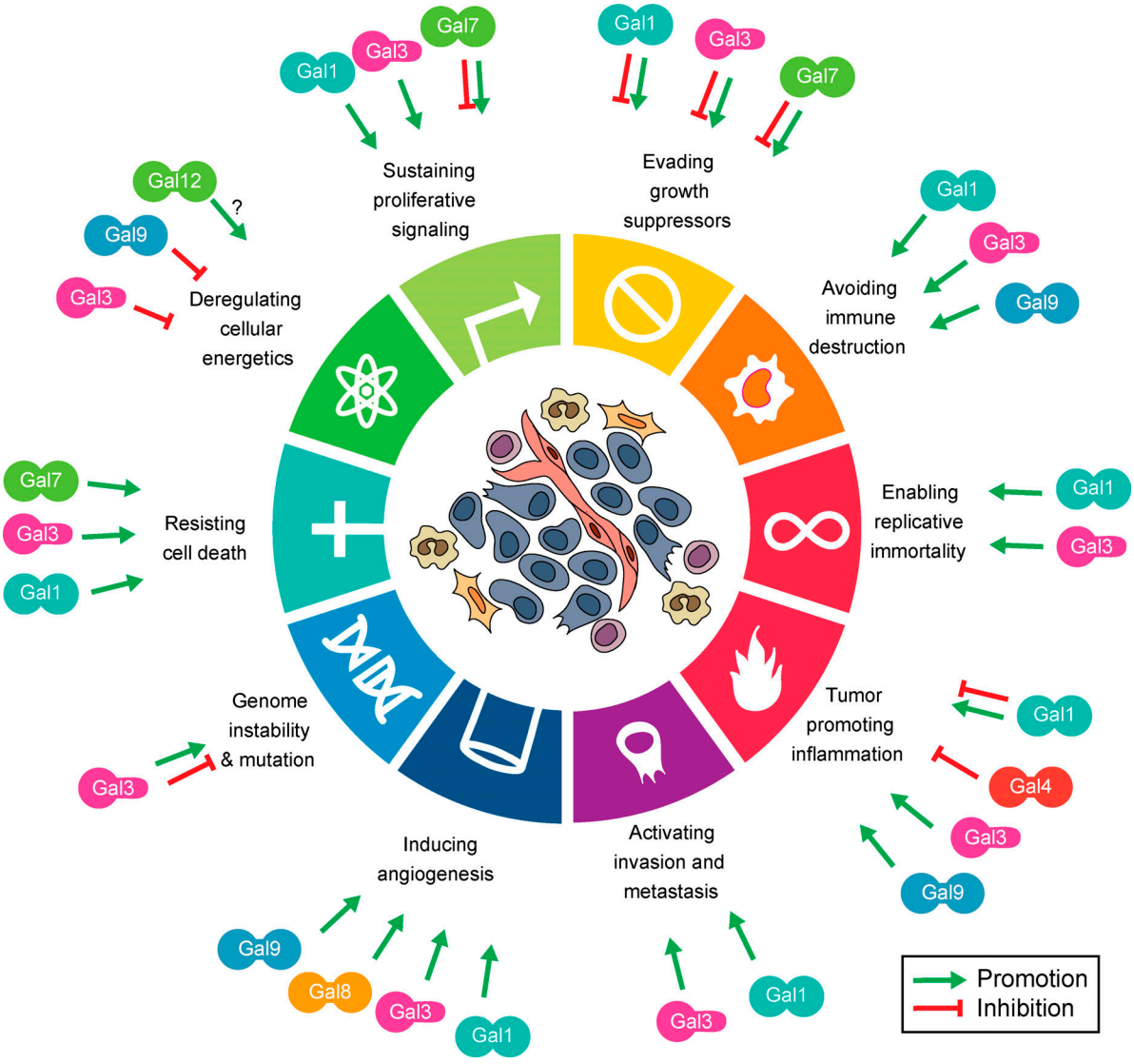

Figure 1. **Role of individual galectins in the hallmarks of cancer.** This adapted figure from Hanahan and Weinberg's iconic review "The hallmarks of cancer: The next generation" (Hanahan and Weinberg, 2011) depicts the impact of different galectin family members on different cancer hallmarks. Galectins can either promote (green) or impair (red) different cellular and molecular processes leading to tumor growth and progression. Most work has focused on the role of galectins on selected cancer hallmarks such as avoiding immune responses, promoting angiogenesis, and sustaining proliferative signaling, while their influence on other hallmarks has only been partially explored. Fig. 1 is adapted with permission from *Cell*.

Glycan modifications, as a result of transcriptional or epigenetic regulation of glycan-modifying enzymes (Munkley and Elliott, 2016), as well as altered expression of glycan-binding proteins (Liu and Rabinovich, 2005), may influence proliferative signaling.

Mutations of the *RAS* gene are one of the most common traits in human cancer. The HRAS, KRAS, and NRAS proteins are constitutively active in cancer cells, promoting continuous proliferation in a variety of tumors (Sanchez-Vega et al., 2018). Both Gal1 and Gal3 can interact with oncogenic RAS proteins on the cell surface, inducing RAS membrane anchorage and activation and influencing tumor cell proliferation (Paz et al., 2001; Elad-Sfadia et al., 2004). Interestingly, in lung cancer, Gal1 interacts with RAS, promoting tumor progression and chemoresistance by up-regulating p38, ERK, and cyclooxygenase-2 (Chung et al., 2012) pathways. On the other hand, evidence indicates that Gal3 promotes tumorigenesis, at least in part, by sustaining KRAS activation. Transfection of Gal3 cDNA into pancreatic ductal adenocarcinoma cells induced augmented RAS activation and amplified downstream signaling events (Song et al., 2012). Moreover, in breast cancer, Gal3 directly activates KRAS, favoring a molecular switch from NRAS to KRAS (Shalom-Feuerstein et al., 2005). Also, in anaplastic thyroid carcinoma, Gal3 serves as a reliable marker of aggressiveness and a scaffold of KRAS protein. In fact, a novel drug combination using the RAS inhibitor salirasib and a modified citrus pectin, which attenuates Gal3 activity, highlights the relevance of KRAS and Gal3 as potential synergistic targets for treating those tumors (Menachem et al., 2015). Unlike Gal1, which augments Ras activation of ERK1/2 at the expense of PI3-K,

Gal3/KRAS–guanosine triphosphate interactions attenuate ERK signaling (Elad-Sfadia et al., 2004), highlighting distinct effects of these lectins during oncogenesis. Further molecular analysis revealed a crucial role of Gal3 in KRAS dependence. Through direct association to integrin $\alpha_v\beta_3$, Gal3 favors KRAS addiction by enabling multiple functions of KRAS in anchorage-independent cells, including the formation of macropinosomes that promote nutrient uptake and control redox balance in lung and pancreatic patient-derived tumor xenografts (Seguin et al., 2017). Additionally, a tumor-promoting effect involving Gal3 and Wnt/β-catenin–dependent pathway has been described in squamous cell tongue carcinoma (Wang et al., 2013), implying the activity of this lectin in multiple signaling pathways.

In contrast to the stimulatory roles of Gal1 and Gal3, Gal7 showed a marked suppressive effect on tumor cell proliferation. Ectopic expression or addition of exogenous Gal7 to human colon cancer cells (Ueda et al., 2004) or neuroblastoma cells (Kopitz et al., 2003) markedly reduced tumor cell proliferation. Mechanistically, Gal7 controlled cell proliferation and differentiation through the modulation of JNK–miR-203–p63 signaling (Chen et al., 2016). Accordingly, in a malignant peripheral nerve sheath tumor, RAS inhibition by salirasib led to reduced Gal1 expression and dramatically increased Gal7 protein, further decreasing RAS activation in tumor cells and rendering them sensitive to apoptosis (Barkan et al., 2013). Interestingly, galectins may also influence cancer cell proliferation by disabling senescence circuitries. This is the case of Gal3, which promotes gastric tumorigenesis by inhibiting premature senescence (Kim et al., 2014). Finally, Gal9 has been reported as a powerful antiproliferative signal on $CD138^+$ multiple myeloma cells (Kobayashi et al., 2010).

Thus, individual members of the galectin family may serve as positive or negative rheostat signals that control tumor cell proliferation by controlling oncogenic signaling or tumor senescence.

Evading growth suppressors

Signals arising from the tumor microenvironment (TME) may also favor tumor growth by promoting the inactivation of tumor suppressors, thus limiting their capacity to halt cell cycle progression (Hanahan and Weinberg, 2011). A dozen of tumor suppressors have been identified so far, with TP53 and retinoblastoma (Rb) being the prototype molecules of this group. These proteins operate as central nodes within complementary circuits that govern the decisions of cells to proliferate or activate senescence and apoptotic programs.

The Rb protein senses the complexity of extracellular factors and conveys this information to the nucleus, where the cell cycle proceeds or is halted until the conditions are optimal. TP53, on the contrary, senses the stress and other nutritional parameters from inside the cell. If those conditions are suboptimal or excessive genome damage is detected, the cell cycle is halted to preserve cell homeostasis or integrity. In human colorectal cancer cells, Gal7 was first identified as an apoptotic/p53-induced gene (PIG1; Polyak et al., 1997). In epidermal keratinocytes, Gal7 expression rapidly increases in response to UVB-induced apoptosis (Bernerd et al., 1999), preventing further damage. Accordingly, Gal7 was proposed as a proapoptotic protein in several cancer cells, including cervical and colon cancer (Ueda et al., 2004). The proapoptotic activity of Gal7, however, was not associated with its ability to interact with glycoconjugates but instead relied on its intracellular function via activation of the JNK pathway and mitochondrial cytochrome c release (Kuwabara et al., 2002). As expected, chemoresistant human urothelial tumors express lower levels of Gal7 compared with normal urothelium. Moreover, transfection with the Gal7 gene (*LGALS7*) sensitized p53-mutated bladder cancer cells to chemotherapy with cis-diamminedichloroplatinum (Matsui et al., 2007). Interestingly, mice lacking Gal7 showed unique defects in the maintenance of epidermal homeostasis in response to injury or environmental challenges (Gendronneau et al., 2008).

The mechanisms underlying Gal7 silencing during oncogenesis include methylation of CpG islands in the *LGALS7* gene and hypermethylation at a region of the exon 2 that is predicted to be a TP53-binding region (Kim et al., 2013a). These shreds of evidence suggest that, when the promoter is inaccessible to TP53 binding (e.g., by methylation), Gal7 expression is silenced. In addition to its intracellular action, which mainly resides within the cytoplasmic compartment, secreted Gal7 interacts with specific glycan residues on the cell surface, mediating extracellular effects. Notably, in neuroblastoma cells Gal7 exerted antiproliferative effects that were dependent on the presence of a permissive glycan profile (i.e., presence of N-acetyl-lactosamine residues) in glycolipids of target cells (Kopitz et al., 2003). Likewise, in head and neck squamous cell carcinoma, hypopharyngeal squamous cell carcinoma, and ovarian serous cystadenocarcinoma, Gal7 expression negatively correlated with disease recurrence (Saussez et al., 2006; Labrie et al., 2014). Nevertheless, the role of Gal7 in cancer appears to be controversial, and some pieces of evidence indicate that Gal7 may also behave as a tumor promoter even when it was originally discovered as a p53-inducible gene. In mice, the development of thymic lymphoma was accelerated when Gal7 was overexpressed, and this effect was accompanied by the expression of prometastatic genes, including metalloproteinases (MMPs), that influenced the aggressive behavior of these tumors (Demers et al., 2005). Likewise, in breast cancer, Gal7 also exhibited a tumor-promoting behavior (Demers et al., 2010). Based on these findings, Campion and colleagues (Campion et al., 2013) sought to explore possible molecular mechanisms that could explain Gal7's paradoxical effects. In silico analysis of the human *LGALS7* promoter revealed the presence of a putative TP53-binding site and several NF-κB–binding sites in the 5′ proximal region, suggesting that both transcription factors may control Gal7 expression. Gain-of-function experiments revealed expression of both WT and mutant TP53 in breast cancer lines MCF-7 and MDA-MB-231, which increased NF-κB activity and up-regulated Gal7 expression. On the contrary, in the p53-null MDA-MB-453 cell line, which exhibited high NF-κB activity, Gal7 was not detectable, indicating that a functional NF-κB–TP53 complex is required to transactivate the *LGALS7* promoter. Also in breast cancer, a reciprocal regulation between Gal7 and TP53 was proposed as Gal7 was able to impede TP53 translocation from the

cytosol to the nucleus, thus counteracting induction of the antiproliferative protein p21 (Grosset et al., 2014). The TP53 status dependency of Gal7 expression in ovarian cancer appears to be even more restricted. Ovarian cancer cells (OVCAR-3) that harbored a $p53^{R248Q}$ mutation expressed Gal7, while cells with a WT p53 or cells with a p53-null genotype did not express this lectin (Labrie et al., 2014).

On the other hand, Gal3 was shown to be transcriptionally repressed by TP53 (Cecchinelli et al., 2006; Raimond et al., 1995), and this was required for TP53-induced apoptosis. Sequencing analysis revealed that the Gal3 gene (*LGALS3*) harbors several consensus regulatory sequences for TP53 binding. When this intronic sequence was inserted in a reporter plasmid, only WT and not mutant p53 down-regulated luciferase activity (Raimond et al., 1995), suggesting that once p53 is mutated, its ability to repress Gal3 is impaired, explaining increased Gal3 expression in p53-mutant tumors (Stiasny et al., 2017). In contrast, in human thyroid tumors, a positive correlation has been found between p53 mutations and Gal3 expression. Those tumors that exhibited the most frequent mutation (p53R273H) and those with p53-null phenotype showed marked up-regulation of Gal3, which conferred chemoresistance to these cells (Lavra et al., 2009). In this regard, TP53-induced apoptosis required phosphorylation of the serine 46 that interacted with coregulator homeodomain-interacting protein kinase 2 (HIPK2), specifically involved in the proapoptotic functions of this protein. HIPK2 cooperates with TP53, mediating transcriptional repression of Gal3. Loss of HIPK2 underlined Gal3 overexpression in well-differentiated thyroid carcinoma, which paradoxically is a p53-sufficient tumor (Lavra et al., 2011). Accordingly, a functional cross-talk among MYCN, TP53, HIPK2, and Gal3 has been reported in experimental neuroblastoma (Veschi et al., 2012).

Convincing evidence of a functional association between Gal1 and TP53 are scarce. Proteomic analysis of glioblastoma cell lines revealed the down-regulation of Gal1 by WT p53 (Puchades et al., 2007); conversely knocking down Gal1 in U87 glioblastoma cells altered expression of cell cycle genes, including p21waf/cip1 and p53 (Camby et al., 2005). On the other hand, Gal3 knockdown in human prostate cancer cells led to a cell cycle arrest at the G1 phase, up-regulation of nuclear p21, and hypophosphorylation of Rb (Wang et al., 2009). Thus, galectins may contribute to evasion of growth suppressors via direct or indirect mechanisms. This effect appears to be critically dependent on the target cell type involved, as well as the severity of stress and/or genomic damage.

Avoiding immune destruction

A critical cancer hallmark relies on the ability of tumor cells to create immunosuppressive microenvironments, thus avoiding immune destruction (Rabinovich et al., 2007). Understanding these immune evasive programs has been instrumental for the design and successful implementation of cancer immunotherapeutic modalities, particularly those targeting the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and the programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) immune checkpoint pathways (Gubin and Schreiber, 2015; Ribas and Wolchok 2018). Galectins are key players in this process by thwarting antitumor immunity through several mechanisms, including promotion of T cell apoptosis, inhibition of T cell activation, induction of anti-inflammatory T helper type 2 (Th2) responses, expansion of $Foxp3^+$ regulatory T (T reg) cells, induction of tolerogenic dendritic cells (DCs), inhibition of natural killer (NK) cell function, and polarization of macrophages toward an M2 phenotype (Rabinovich and Toscano, 2009; Méndez-Huergo et al., 2017). In a melanoma model, targeting Gal1 enhanced tumor rejection by enhancing Th1 and CTL responses, suggesting that Gal1 contributes to tumor-immune privilege (Rubinstein et al., 2004). Accordingly, in tumor specimens from head and neck squamous cell carcinoma patients, Gal1 overexpression inversely correlated with the number of infiltrating T cells and was an independent prognostic factor for shorter overall survival (Le et al., 2005). Moreover, in neuroblastoma, Gal1 acted as an immunosuppressive factor that compromised T cell and DC functions (Soldati et al., 2012). Likewise, Gal1 secreted by human pancreatic stellate cells (PSCs) induced T cell apoptosis and contributed to Th2 cytokine polarization, fostering immune privilege in the pancreatic TME (Tang et al., 2012; Orozco et al., 2018). Remarkably, genetic deletion of the Gal1 gene (*Lgals1*) in a *Kras*-driven model of pancreatic ductal adenocarcinoma (*Ela-KrasG12Vp53*$^{-/-}$) led to a significant increase in mice survival and reduced metastasis through mechanisms involving greater T cell infiltration (Orozco et al., 2018). Mechanistically, Gal1 exerts selective inhibitory effects on Th1 and Th17 cells due to differential glycosylation of cell surface receptors on these T cell subsets (Toscano et al., 2007), thus providing a rational explanation for Gal1-polarized T cell responses. In this regard, Th2 cells were protected from Gal1 action by exposing a glycan shield composed of α2,6-linked sialic acid (Toscano et al., 2007). Supporting these findings, Reed-Sternberg cells in classical Hodgkin lymphoma express high amounts of Gal1 through mechanisms involving activation of the AP-1 transcription factor, favoring a Th2-dominant immunosuppressive microenvironment (Juszczynski et al., 2007). Moreover, in a breast cancer model, Gal1 promotes the expansion of $Foxp3^+$ T reg cells within the TME, draining lymph nodes, and lung metastases (Dalotto-Moreno et al., 2013). In addition, this lectin favors differentiation of tolerogenic DCs characterized by high CD45RB expression, STAT-3 phosphorylation, and secretion of IL-27 and IL-10; this effect accelerated tumor growth in the B16 melanoma model (Ilarregui et al., 2009). Of note, Gal1 is a key mediator of tumor-educated DCs controlled by the SATB-1 transcription factor (Tesone et al., 2016). On the other hand, blockade of Gal1 expression in glioma cells augmented NK cell–mediated cytotoxicity promoting tumor eradication (Baker et al., 2014), suggesting multiple inhibitory effects of this lectin on different innate and adaptive immune cells. In this regard, Gal1 induced deactivation of macrophages and microglia through O-glycosylation–dependent mechanisms targeting CD45 phosphatase activity (Correa et al., 2003; Barrionuevo et al., 2007; Starossom et al., 2012). Targeting glioma-derived Gal1 decreased the number of brain-infiltrating macrophages (Verschuere et al., 2014), highlighting a central role for myeloid cells as key targets of the

immunoregulatory activity of this lectin. In this regard, granulocytic myeloid-derived suppressor cells as well as γδ-T cells accelerated malignant progression via secretion of Gal1 in models of ovary cancer (Rutkowski et al., 2015; Rabinovich and Conejo-García, 2016), suggesting different sources of this lectin in the TME. Interestingly, antibody-mediated Gal1 blockade or manipulation of the N-glycosylation machinery promoted influx and activation of tumor-specific $CD8^+$ T cells (Croci et al., 2014). More recently, Gal1 has been implicated in T cell exclusion in the TME of head and neck squamous carcinoma (Nambiar et al., 2019).

On the other hand, tumoral Gal3 promoted CTL dysfunction and impaired IFN-γ secretion by forming glycan-dependent lattices that distanced TCR from CD8 molecules (Demotte et al., 2008). This effect was abrogated by GCS-100, a galectin-inhibitory polysaccharide (Demotte et al., 2010). More recent studies showed that tumor-secreted Gal3 traps both glycosylated IFN-γ and extracellular matrix glycoproteins, thus preventing the formation of IFN-γ–induced chemokine gradients required for T cell infiltration (Gordon-Alonso et al., 2017). This effect could be critical in dictating T cell exclusion in immunologically desert tumors. Furthermore, Gal3 has been proposed to function as a LAG-3 extracellular ligand promoting CD8 T cell dysfunction and limiting the expansion of plasmacytoid DCs (Kouo et al., 2015). Interestingly, anti–CTLA-4 therapy elicited the presence of circulating anti-Gal3 antibodies in patients with metastatic melanoma (Wu et al., 2018), highlighting the clinical relevance of this lectin in resistance to immunotherapy. Moreover, tumor-derived Gal3 reduces the affinity of MHC class I–related chain A for NKG2D (Tsuboi et al., 2011) and serves as a soluble inhibitory ligand for human NKp30 (Wang et al., 2014), suggesting an additional role for this lectin in limiting NK cell attack.

Finally, Gal9, a tandem-repeat member of the galectin family, promotes immune escape through T cell immunoglobulin and mucin domain-containing 3 (TIM-3)–dependent or independent pathways (Sakuishi et al., 2011). Whereas Gal9 impairs NK cell cytotoxicity through association with TIM-3 in acute myeloid leukemia (Gonçalves Silva et al., 2017), this lectin promotes immune tolerance in pancreatic cancer via a TIM-3–independent pathway involving ligation of Dectin-1, a C-type lectin receptor on macrophages (Daley et al., 2017). Additionally, Gal9 promotes differentiation of $CD11b^+Ly\text{-}6G^+$ regulatory myeloid-derived suppressor cells through interaction with TIM-3 (Dardalhon et al., 2010) but enhances the stability and function of T reg cells through association with CD44 (Wu et al., 2014). In addition, a dynamic Gal3–N-glycan lattice enhances the T cell activation threshold (Demetriou et al., 2001), reinforcing the immune inhibitory activity of these multivalent signaling complexes. Hence, through binding to distinct glycosylated receptors on immune cells, individual members of the galectin family, particularly Gal1, Gal3, and Gal9 may dampen antitumor immunity by influencing lymphoid and myeloid programs. Thus, targeting specific galectins and their glycosylated ligands, either alone or in combination with other antitumor strategies, emerges as a potential immunotherapeutic modality, warranting the development of preclinical and clinical trials (Chou et al., 2018). Moreover, these lectins could function as possible clinical biomarkers. Supporting this notion, recent studies showed that Gal3 expression may predict response to immune checkpoint blockers in non-small cell lung carcinoma settings (Capalbo et al., 2019).

Enabling replicative telomerase

A critical feature of cancer cells is their capacity to overcome normal senescence resulting from telomeres shortening. Telomerase activation is a critical step in carcinogenesis, occurring in >90% of cancers (Harley et al., 1994). Since transcriptional reactivation of the human telomerase reverse transcription (*hTERT*) gene is a major mechanism of cancer-specific telomerase activation, suppression of hTERT expression emerges as a robust approach for cancer therapy (Jäger and Walter, 2016). Although evidence of the role of galectins in this cancer hallmark is limited, knocking down Gal3 decreased expression of hTERT in gastric cancer cells, inducing cellular senescence. Of note, Gal3 has been proposed to physically interact with hTERT through its N-terminal domain, regulating its telomeric activity during gastric tumorigenesis (La et al., 2016). Moreover, a possible link has been described between Gal1 and hTERT in multiple myeloma cells (Panero et al., 2014). Further studies are warranted to explore the possible association of galectins and telomeres during the tumorigenic process.

Tumor-promoting inflammation

Tumor-associated inflammatory responses involve secretion of multiple pro-inflammatory cytokines, chemokines, and growth factors that promote epithelial cell proliferation, fibroblast recruitment, and neovascularization (Arnold et al., 2015). Chronic inflammation may thus contribute to tumor development and progression, helping incipient lesions to acquire cancer hallmarks capabilities (Coussens et al., 2013). Different galectin family members may help tip the balance of an inflammatory response, altering tissue homeostasis. Epithelial-derived Gal4 amplifies IL-6-dependent inflammatory responses, thus influencing mucosal homeostasis (Hokama et al., 2004). In addition, Gal4 can stimulate memory $CD4^+$ T cell expansion under particular inflammatory conditions via interaction with immature core 1-expressing O-glycans, generated as a result of down-regulation of the core-2 β1,6-N-acetylglucosaminyltransferase 1 (Nishida et al., 2012), thus counteracting tumor progression. Accordingly, this lectin functions as a potent tumor suppressor of human colorectal cancer (Satelli et al., 2011). Inhibition of Gal4 expression promoted cancer cell proliferation via activation of IL-6/NF-κB/STAT-3 signaling (Kim et al., 2013b). Thus, Gal4 recalibrates the TME in the gut through regulation of cancer-associated inflammatory responses modulating both immune and epithelial compartments. Interestingly, in a model of chronic liver inflammation leading to hepatocellular carcinoma, lack of Gal1 increased liver injury, inflammation, and fibrosis, at early age. Moreover, aged knockout mice displayed earlier hepatocarcinogenesis and increased tumor growth. The mechanisms underlying these effects revealed modulation of pro-oncogenic cytokines, including osteopontin, Ntrk2 (TrkB) and S100A4 as critical targets of Gal1 activity (Potikha et al., 2019). Conversely, in ovary cancer models Gal1 contributes to

tumor-promoting inflammation linking TLR5-dependent IL-6 production and distant tumor progression (Rutkowski et al., 2015). Interestingly, augmented Gal2, Gal4, and Gal8 in sera from cancer patients enhanced the circulation of G-CSF, IL-6, and MCP-1, suggesting a cross-talk among galectins, pro-inflammatory cytokines, and chemokines (Chen et al., 2014).

Through secretion of growth factors and cytokines, cancer-associated fibroblasts (CAFs) have a critical role in tumor development and progression (Kalluri, 2016). Recent studies revealed that Gal1 released by human PSCs caused the progression of preneoplastic pancreatic lesions. PSC-derived Gal1 promoted cyclin D–dependent epithelial cell proliferation as well as expression of tissue remodeling proteases and proangiogenic factors (Orozco et al., 2018). Moreover, this lectin triggered Hedgehog pathway signaling in pancreatic ductal adenocarcinoma–associated fibroblasts (Martínez-Bosch et al., 2014).

On the other hand, Gal3 has been proposed to be a key pro-inflammatory mediator during the initial steps of the metastatic cascade, linking inflammation and endothelium permeability. Mechanistically, Gal3 stimulates secretion of IL-6 and G-CSF, leading to up-regulated expression of metastasis-associated adhesion molecules, including integrin $\alpha_V\beta_1$, vascular cell adhesion molecule-1, and E-selectin (Chen et al., 2013). Moreover, Gal9 binds to CD206 on macrophages and stimulates the release of fibroblast growth factor 2 and MCP-1, thus supporting tumor growth (Enninga et al., 2018). Thus, galectins may serve as critical mediators of tumor-promoting inflammation acting both at the initial stages of tumor development and during the metastatic cascade.

Activating invasion and metastasis

Metastasis is the result of a multistage sequence of limiting events called the metastatic cascade, meaning that if one step is blocked, the whole process is compromised. This process involves invasion of tumor cells to the surrounding tissue, intravasation, survival in the circulation, extravasation, and colonization of targeted organs. The success of each step, during early or late dissemination, relies on a multiplicity of factors hierarchically regulated at the transcriptional and posttranscriptional levels (Hanahan and Weinberg, 2011). Particularly interesting are emerging mechanisms leading to early tumor cell dissemination, dormancy, and tissue colonization as determinant factors of metastasis (Sosa et al., 2014). Galectins significantly impact this hallmark by regulating metastasis-related events. In fact, Gal3 was early identified as a metastasis-related protein involved in tumor invasion (Bresalier et al., 1998). In clinical settings, Gal1, Gal3, and Gal4 levels were found to be considerably higher in sera from patients with metastatic disease than in patients with localized tumors and healthy individuals (Iurisci et al., 2000), suggesting the utility of these lectins as possible biomarkers of disseminated disease. Interestingly, elevated Gal3 expression was associated with increased anchorage-independent growth, homotypic and heterotypic aggregation, and target organ colonization (Nangia-Makker et al., 2012). In fact, Gal3 released by tumor cells regulates invasion and motility by weakening interactions between cell adhesion molecules present on the surface of malignant cells and N-glycosylated proteins within the extracellular matrix, including laminin and fibronectin (Nangia-Makker et al., 2008). In this sense, this lectin promotes adhesion of breast cancer cells to the endothelium by interacting with cancer-associated Thomsen-Friedenreich galactose β-1,3-N-acetylgalactosamine 2 antigen expressed on MUC1 (Yu et al., 2007), thus favoring intravasation and extravasation processes. On the other hand, tumor-derived Gal3 associates with the N-glycosylated ligand CD146 expressed on endothelial cells (ECs; Colomb et al., 2017) and induces the release of metastasis-promoting pro-inflammatory cytokines (Chen et al., 2013). Notably, the activity of Gal3 at metastatic sites is regulated by the glycan profile of tumor cells. Tumor cells with low expression of α-N-acetylgalactosaminide α-2,6-sialyltransferase 2 show enhanced binding of soluble Gal3, which promotes homotypic and heterotypic aggregation, facilitating emboli formation and metastasis (Murugaesu et al., 2014). Moreover, in renal cell carcinoma, Gal3 augments stemness and progression via up-regulation of the CXCR2 chemokine (Huang et al., 2018), whereas in lung cancer, Gal3 contributes to metastatic niche formation through binding to Thomsen-Friedenreich antigen on metastatic tumor cells (Reticker-Flynn and Bhatia, 2015).

Gal1 also promotes homotypic and heterotypic aggregation (Lotan et al., 1994; Tinari et al., 2001) by interacting with laminin and fibronectin (van den Brûle et al., 2003) and delineates the metastatic potential of several human tumors (Liu and Rabinovich, 2005). Interestingly, stromal cell expression of Gal1 is up-regulated in invasive breast carcinoma as compared with in situ carcinoma, showing a positive correlation with T (related to tumor size) or TNM (dissemination to nodes or metastatic sites) progression stages (Jung et al., 2007). Moreover, Gal1 expression in CAFs correlated with enhanced regional lymph node breast cancer metastasis (Folgueira et al., 2013). Investigation of the mechanisms underlying Gal1 promotion of tumor invasion in oral squamous cell carcinoma (OSCC) revealed the ability of this lectin to up-regulate MMP-2 and MMP-9 and reorganize actin cytoskeleton via activation of Cdc42, a small GTPase member of the Rho family, thus increasing the number and length of filopodia on tumor cells. Targeting this lectin in CAFs inhibited OSCC invasion and metastasis (Wu et al., 2009). Accordingly, Gal1 expression in cancer-associated stroma significantly correlated with poor prognosis in OSCC (Chiang et al., 2008). Further, in gastric cancer, high Gal1 expression in CAFs facilitated cancer cell migration and invasion by up-regulating β_1-integrin expression (He et al., 2014) and inducing epithelial-to-mesenchymal transition (EMT) via non-canonical activation of the Hedgehog pathway (Chong et al., 2016). Likewise, in hepatocellular carcinoma, Gal1 facilitated the transition from epithelial morphology toward a fibroblastic phenotype by up-regulating mesenchymal markers and down-regulating E-cadherin expression (Bacigalupo et al., 2015). Moreover, in human pancreatic cancer, Gal1 acts as a major metastasis driver by triggering EMT via NF-κB transcriptional regulation and inducing significant overexpression of invasion- and migration-associated genes, including MMP1, S100A7, and ankyrin-3 (Tang et al., 2017; Orozco et al., 2018). Moreover, Gal1 silencing significantly inhibited migration and invasion of

metastatic castration-resistant prostate cancer through suppression of androgen receptor and Akt signaling (Shih et al., 2018), thus emphasizing the prometastatic activity of this lectin through diverse partially overlapping mechanisms. In this regard, Gal1 has been identified as a key effector of tropomyosin receptor kinase–mediated invasiveness and migration in neuroblastoma (Cimmino et al., 2009). Finally, in human prostate cancer xenografts, Gal4 binding to receptor tyrosine kinases activated expression of phospho-ERK, phospho-Akt, and Twist and lowered expression of E-cadherin, thus facilitating EMT (Tsai et al., 2016). Thus, galectin–glycan interactions may control invasion, dissemination, and colonization programs broadly influencing the choreography of metastasis-related players, including signaling pathways, transcription factors, chemokines, and cell adhesion molecules.

Inducing angiogenesis

Angiogenesis, the growth of new blood vessels out of preexisting ones, is an essential requirement in the development and progression of cancer. Genetic and pharmacological inhibition of vascular signaling pathways have provided critical evidence that abnormal angiogenesis is a hallmark of cancer (Ferrara and Kerbel, 2005; Potente et al., 2011). Galectins play essential roles at different steps of the angiogenic cascade (Thijssen et al., 2013). Both tumors and stromal cells can stimulate aberrant angiogenesis by secreting Gal1 (Thijssen et al., 2006, 2010; Croci et al., 2012; Laderach et al., 2013). Uptake of Gal1 by ECs promote HRAS signaling to the RAF/mitogen-activated protein kinase/ERK cascade and stimulate EC proliferation and migration (Thijssen et al., 2010). Moreover, interactions between Gal1 and specific N-glycans couple tumor hypoxia to neovascularization in Kaposi sarcoma through hypoxia-inducible factor–independent, NF-κB–dependent mechanisms (Croci et al., 2012).

Gal3 also promotes angiogenesis by modulating vascular endothelial growth factor (VEGF) and basic fibroblast growth factor signaling through binding to complex N-glycans on integrin $\alpha_v\beta_3$ (Markowska et al., 2010). This effect appears to be dependent on the Notch ligand JAG1 (Dos Santos et al., 2017). Finally, whereas Gal8 induces angiogenesis through binding to activated leukocyte cell adhesion molecule (CD166) on ECs (Delgado et al., 2011), different Gal9 isoforms selectively control vascularization through still-unknown mechanisms (Aanhane et al., 2018).

In the past decade, the first generation of antiangiogenic drugs has been validated in clinical settings, showing improved progression-free survival and, in some cases, overall survival in patients with different tumor types. Tyrosine kinase inhibitors, as well as specific monoclonal antibodies, disrupt angiogenesis through inhibition of VEGF and their cognate receptors (Ferrara and Kerbel, 2005). Although preclinical and clinical studies revealed satisfactory outcomes in tumor growth inhibition, anti-VEGF therapy has shown limited efficacy. Several tumors develop resistance through the activation of compensatory pathways that contribute to tumor angiogenesis. Through recognition of complex N-glycans on VEGFR2, Gal1 activates a glycosylation-dependent compensatory mechanism that preserves angiogenesis in response to VEGF blockade (Croci et al., 2014). Gal1 triggers VEGF-like signaling, including phosphorylation of VEGFR2, ERK1/2, and Akt in ECs. Vessels within anti-VEGF–sensitive tumors exhibited high levels of α2,6-linked sialic acid, which prevented Gal1 binding and compensatory angiogenesis. In contrast, anti-VEGF–refractory tumors secreted Gal1 in response to hypoxia, and their associated vasculature displayed glycosylation patterns that were permissive for Gal1–EC interactions. Interruption of β1-6GlcNAc branching on ECs or silencing of tumor-derived Gal1 converted refractory into anti-VEGF–sensitive tumors, whereas elimination of α2,6-linked sialic acid conferred resistance to anti-VEGF. Disruption of the Gal1–N-glycan axis promoted vascular remodeling, immune cell influx, and tumor growth inhibition, thereby increasing the efficacy of anti-VEGF treatment (Croci et al., 2014). Thus, glycosylation-dependent galectin-driven mechanisms control blood vessel formation through VEGF-dependent or independent mechanisms involving distinct glycosylated receptors and signaling pathways.

Acquiring genome instability

Cells may acquire random mutations and chromosomal rearrangements that contribute to tumor development and progression. Specific mutant genotypes confer a selective advantage on tumor subclones, enabling their outgrowth and eventual dominance in a local tissue environment (Hanahan and Weinberg, 2011). The role of genome maintenance machinery is to detect and resolve DNA defects, ensuring low rates of spontaneous mutations during each cell generation (Lane, 1992). Interaction of Gal3 with BARD1, the main partner of breast and ovarian cancer susceptibility gene product BRCA1, has been documented, suggesting involvement of these proteins in the DNA damage repair machinery. Knocking down Gal3 increased resistance to DNA damage in HeLa cells, leading to the identification of a set of four Gal3 partners associated with DNA damage repair, namely PARP1, HSP90AB1, CDC5L, and PRPF19 (Carvalho et al., 2014). Likewise, a comparative analysis considering microsatellite stability in clinical specimens of colon cancer revealed enrichment of Gal3 in microsatellite-stable compared with microsatellite-unstable tumors (Gebert et al., 2012). Although much remains to be learned, intracellular galectins may serve as a link between genomic instability and tumorigenesis.

Developing resistance to cell death

Cancer cells acquire the ability to escape death triggered by cell surface receptors, soluble factors, immune effector cells, and anticancer therapies, thus facilitating tumor progression (Hanahan and Weinberg, 2011). Galectins may interact with different components of the extrinsic and intrinsic apoptotic machineries, thus influencing tumor cell fate (Lichtenstein and Rabinovich, 2013).

Pioneer work demonstrated a significant intracellular role for Gal3 in conferring resistance to apoptosis induced by anti-Fas antibody, staurosporine, and cisplatin. Strikingly, Gal3 was found to have significant sequence similarity with Bcl-2, a well-characterized antiapoptotic gene (Yang et al., 1996; Akahani et al., 1997). Further studies showed that Gal3 represses

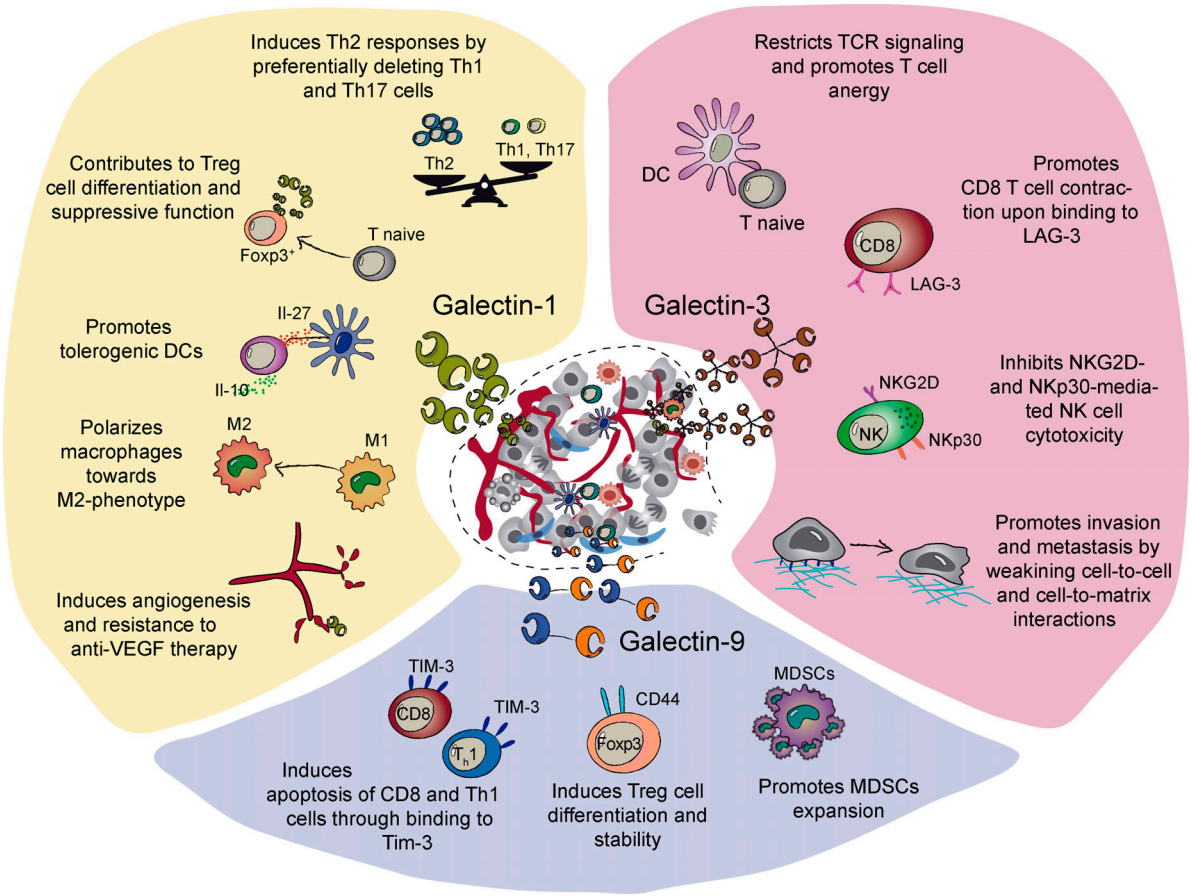

Figure 2. **Galectin-driven regulatory circuits in the TME.** Galectins influence the function of distinct cell types, including immune cells, ECs, and CAFs in the TME. Within the immune compartment, Gal1, Gal3, and Gal9 fuel immune-evasive mechanisms through the control of myeloid and lymphoid programs. Gal1 tilts the balance of the immune response toward a Th2 profile by selectively deleting Th1, Th17, and CTLs. Moreover, Gal1 drives the differentiation of T reg cells, endows DCs with tolerogenic potential, polarizes macrophages toward an anti-inflammatory M2 profile, and inhibits NK cell function. Interestingly, Gal1–N-glycan interactions may couple tumor hypoxia to vascularization and preserve angiogenesis in tumors refractory to anti-VEGF treatment. On the other hand, Gal3 acts by limiting TCR-dependent signaling and promoting T cell anergy and exhaustion by distancing the TCR from CD8 molecules and engaging LAG-3 on the surface of CD8 T cells. Gal3 also impairs the antitumor activity of NK cells by inhibiting NKp30-mediated cytotoxicity and interrupting NKG2D–MHC class I–related chain A interactions. Moreover, Gal3 influences VEGF and basic fibroblast growth factor–induced angiogenesis through binding to N-glycan motifs on $\alpha_v\beta_3$ integrin. Moreover, Gal9 confers immune privilege to tumor cells through TIM-3–dependent or independent mechanisms. While it selectively kills terminally differentiated TIM-3$^+$ Th1 cells, it also binds to Dectin-1 on macrophages and CD44 on T reg cells, favoring a tolerogenic microenvironment. On the other hand, Gal8 controls EC biology via association with ALCAM-1 (CD166), whereas different Gal9 isoforms selectively control angiogenesis. Within the tumor stroma, Gal1 is highly expressed in CAFs, particularly in human stellate pancreatic cells and controls fibroblast secretion of a variety of cytokines, chemokines, and growth factors. Gal1 (a prototype family member) is indicated as a noncovalent homodimer each containing one CRD, Gal3 (a chimera-type galectin) is illustrated based on its pentameric structure, and Gal9 (a tandem-repeat galectin) is depicted as two CRDs connected in tandem. MDSC, myeloid-derived suppressor cell.

apoptotic signals by associating with Fas/CD95, thus increasing tumor cell survival (Fukumori et al., 2004). When Gal3 is overexpressed in bladder carcinoma cells, it promotes Akt phosphorylation and confers resistance to tumor necrosis factor–related apoptosis-inducing ligand–induced apoptosis. Moreover, this lectin protects tumor cells from apoptosis by enhancing cell adhesion properties (Matarrese et al., 2000), and its phosphorylation is critical to control tumor survival (Yoshii et al., 2002). This effect confers cell death resistance in a variety of cancers, including diffuse large B cell lymphoma (DLBC; Hoyer et al., 2004) and breast adenocarcinoma (Matarrese et al., 2000). Although these prosurvival effects involve mostly an intracellular activity of this lectin, Clark et al. (2012) identified an anti-apoptotic function of Gal3 through binding to specific O-glycans on CD45 at the surface of DLBC. Moreover, targeting Gal1 expression in glioblastoma increased sensitivity to chemotherapeutic agents (Le Mercier et al., 2008), particularly, temozolomide both in vitro and in vivo. Likewise, silencing Gal1 in melanoma sensitized cells to the proautophagic effects of temozolomide (Mathieu et al., 2007). In this regard, Gal1 conferred chemoresistance in hepatocellular carcinoma by regulating the autophagic machinery (Su et al., 2016). However, in contrast to Gal3 and Gal1, Gal7 showed clear proapoptotic activity against several cancer cell types (Barkan et al., 2013; Ueda et al., 2004; Higareda-Almaraz et al., 2016; Kuwabara et al., 2002). Accordingly, Gal7 sensitized tumor cells to cisplatin treatment by promoting the accumulation of intracellular reactive oxygen species and activation of the JNK pathway (Matsui et al., 2007). Finally,

recent studies showed an inverse correlation between Gal3 expression and the extent of tumor necrosis in renal cell carcinoma patients (Aboulhagag et al., 2018). Thus, intracellular galectins may govern cell death pathways, including apoptosis, necrosis, or autophagy, induced by pro-inflammatory cytokines, reactive oxygen species, and anticancer agents.

Deregulating cellular energetics

Acquisition of tumorigenic and metastatic capabilities requires a well-adjusted energy metabolism that fuels tumor growth. Unlike normal cells that metabolize glucose entirely into carbon dioxide and maximize ATP production through oxidative phosphorylation, cancer cells may coopt a less efficient process termed aerobic glycolysis. Otto Warburg initially described the abnormal energy metabolism of cancer cells, which even in the presence of oxygen metabolize glucose incompletely into lactate (Koppenol et al., 2011). This apparent counterintuitive energy production route in combination with an increased glutamine metabolism provides tumor cells with the building blocks required to sustain protein, lipid, and nucleic acid synthesis necessary for an accelerated division rate, constituting a distinct cancer hallmark (Cantor and Sabatini, 2012).

Although glycosylation has emerged as a major regulator of metabolic fitness in the TME (Song et al., 2018), scarce information is available regarding the role of glycan-binding proteins in this process. The glycolytic pathway promotes N-glycan branching by fueling metabolites into the hexosamine pathway, thus increasing the number of galectin ligands on relevant cell-surface receptors (Partridge et al., 2004). Although Gal3 cross-links complex branched N-glycans on epidermal growth factor and TGF-β receptors at the surface of breast cancer cells and favors cytokine signaling, EMT, cell motility, and tumor metastasis (Partridge et al., 2004), scarce information is available on the role of galectin-glycan lattices in tumor metabolism.

In this regard, Gal9 has been shown to bind to N-glycans on TIM-3 in myeloid leukemia cells, interrupting mammalian target of rapamycin (mTOR) signaling, hampering glycolysis, and inhibiting tumor cell proliferation (Gonçalves Silva et al., 2017). Moreover, intracellular Gal3 interacts with the ATP synthase in mitochondria of colorectal cancer cells, limiting ATP production and mitochondrial respiration (Lee et al., 2013). On the other hand, Gal12 may influence mitochondrial activity in adipocytes, although its role in tumor metabolism remains to be elucidated (Yang et al., 2011). Given the elevated expression of galectins in the TME, it is anticipated that they play a significant role in tumor cell energetics, linking metabolism-dependent glycosylation status with tumor malignancy and progression.

Conclusions and future perspectives

Galectins contribute to tumor progression through multiple interconnected pathways (Fig. 2). Given their critical roles in different hallmarks of cancer, galectins have emerged as relevant therapeutic targets and reliable biomarkers delineating clinical responses and patient prognosis.

The last two decades have witnessed a paradigm shift in the field of cancer therapy leading to the development of immunotherapies, targeted therapies, and antiangiogenic therapies. However, durable responses are only observed in a limited number of patients due to intrinsic resistance mechanisms and acquisition of compensatory pathways. Combination therapies may enhance the quality of clinical responses (i.e., response duration, progression-free survival, and overall survival) in cancer patients by combining agents with synergistic mechanisms of action. In this promising scenario, galectins have emerged as novel therapeutic targets to be taken into account for combinatorial modalities. However, it is still not clear whether extracellular or intracellular activities of galectins should be preferentially targeted to halt tumor progression. Importantly, although some findings presented here are based on overexpression of galectins in mouse models and human cancer cell lines, these studies could have limitations in their translation to clinical settings, suggesting the need of further preclinical and clinical work to validate the therapeutic relevance of these glycan-binding proteins. In fact, numerous efforts are underway to develop effective galectin-targeted anticancer compounds, mainly represented by chemical inhibitors, natural polysaccharides, peptidomimetics, and monoclonal antibodies (Cagnoni et al., 2016), that could effectively control different hallmarks of cancer.

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