Galectins in hematological malignancies

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Purpose of review
Galectins are a family of lectin molecules that have emerged as key players in inflammation and tumor progresssion by displaying intracellular and extracellular activities. This review describes the recent advances on the role of galectins in hematological neoplasms.

Recent findings
Galectin-1 and galectin-3 are the best studied galectins in oncohematology. Increased expression of galectin-1 has been associated with tumor progression in Hodgkin's lymphoma and chronic lymphocytic leukemia, whereas galectin-3 plays a supporting role in chronic myelogenous leukemia and multiple myeloma. Functional studies have assigned a key role for galectin-1 as a negative regulator of T-cell immunity in Hodgkin's lymphoma and cutaneous T-cell lymphoma. Of therapeutic interest is the development of agents with the capacity to interfere with galectin functions.

Summary
Current knowledge indicates a key role for galectins in hematological neoplasms by favoring the growth and survival of tumor cells and facilitating tumor immune escape. Intervention using specific galectin inhibitors is emerging as an attractive therapeutic option to alter the course of these malignancies.

Keywords
galectins, Hodgkin's lymphoma, lymphomas, myeloma, non-Hodgkin's lymphoma

INTRODUCTION

Multivalent interactions between endogenous lectins and specific N-glycans and O-glycans generated by the synchronized action of glycosyltransferases and glycosidases have emerged as key regulators of inflammation and tumor progression [1]. Among the diverse lectin families, galectins are probably the most conserved and ubiquitous [2]. Galectins act in the extracellular milieu by interacting with a myriad of cell-surface glycosylated receptors [2]. However, these lectins also display intracellular activities including modulation of signaling and splicing machineries [3]. They are classified into 'proto-type' galectins (galectin-1, galectin-2, galectin-5, galectin-7, galectin-10, galectin-11, galectin-13, galectin-14 and galectin-15), which have one carbohydrate recognition domain (CRD) and can dimerize; 'tandem-repeat' galectins (galectin-4, galectin-6, galectin-8, galectin-9 and galectin-12), which contain two homologous CRDs in tandem in a single polypeptide chain; and galectin-3, which is unique as it contains a CRD connected to a nonlectin N-terminal region that is responsible for oligomerization (Fig. 1). Although originally defined by their ability to recognize the common disaccharide Galβ1–4 GlcNAc (LacNAc), considerable differences exist in the glycan-binding preferences of individual members of the galectin family, which might explain the differences in biological activities [4]. Although some galectins are widely expressed in a variety of cells and tissues (e.g. galectin-1, galectin-3 and galectin-9), others have a more restricted tissue localization. For example, galectin-10 appears to be restricted to eosinophils and $CD4^+CD25^+$ T regulatory (T_{reg}) cells and galectin-7 is preferentially expressed in the stratified epithelium [1].

Research over the last years has illuminated essential functions of galectins in receptor

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KEY POINTS

- Galectins, a family of endogenous glycan-binding proteins, play key roles in tumor progression, including hematologic malignancies.
- Galectin-1 plays a negative regulatory role in Hodgkin's lymphoma and cutaneous T-cell lymphoma, whereas it has a prosurvival and activating factor in chronic lymphocytic leukemia.
- Overexpression of galectin-3 in diffuse large B-cell lymphoma and chronic myelogenous leukemia confers resistance to genotoxic agents.
- Galectin-9 derived from the acute myelogenous leukemia cells induces T-cell dysregulation and facilitates tumor progression.
- Selective blockage of galectins holds promise as a treatment option for hematologic neoplasms.

reorganization, turnover and signaling, thus dictating the choice among cell proliferation, differentiation and survival. By positively or negatively regulating these processes, galectin–glycan interactions can sustain the formation of microenvironmental niches during hematopoiesis, modulate acute and chronic inflammatory responses, and provide 'on-and-off' signals that control the decisions between immune cell responsiveness and tolerance [1,5]. For example, galectin-1 suppresses chronic inflammation, blunts Th1 and Th17 responses, and skews the immune response toward a Th2-type cytokine profile [6]. In addition, this lectin instructs dendritic cells to become tolerogenic [7], induces alternatively activated 'M2-type' macrophages and microglia [8], and favors the expansion of FoxP3^{+} T regulatory (T_{reg}) cells and FoxP3$^{(-)}$ type-1 T_{reg} (Tr1) cells [9,10▪], further limiting the magnitude of an effective immune response. On the other hand, galectin-3 can positively or negatively regulate T-cell survival, cytokine balance and dendritic cell immunogenicity [3], leading to either amplification or termination of inflammatory responses. These divergent functions may depend on whether this lectin works in intracellular or extracellular compartments. Moreover, galectin-9 has been identified as a major binding partner for the inhibitory receptor TIM-3 which activates tolerogenic circuits that halt Th1 cell responses [11], but can also lead to dendritic cell activation and stimulation of innate immunity [12].

Current research indicates that galectins are upregulated or downregulated in tumor microenvironments and have important roles in cancer; they contribute to neoplastic transformation, tumor cell survival and tumor metastasis [3,13]. Additionally, they can create immunosuppressive networks that thwart antitumor responses by selectively blunting tumor-specific T-cell responses, promoting the recruitment and expansion of T_{reg} cells and shifting the cytokine balance toward an anti-inflammatory response [9,14–18]. Moreover, galectins (particularly galectin-1, galectin-3 and galectin-8) serve as key mediators of hypoxia-driven tumor cell angiogenesis [19–25]. Thus, galectins affect tumor progression through multiple mechanisms operating directly on cancer cells or indirectly in the tumor microenvironment (Fig. 2). These autocrine and paracrine effects have been widely studied in solid tumors; yet, information on hematologic malignancies is just emerging. Here, we aim to integrate scattered information on the role of galectins in hematological malignancies of both lymphoid and myeloid origins.

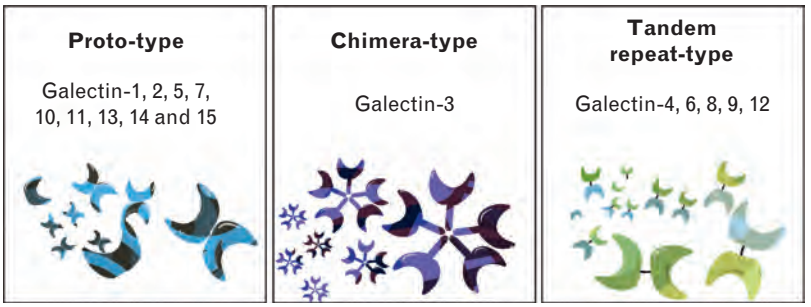

FIGURE 1. Schematic representation of the structures of distinct members of the galectin (Gal) family. Galectins can be subdivided into three groups: 'proto-type' galectins (including Gal-1, Gal-2, Gal-3, Gal-5, Gal-7, Gal-10, Gal-11, Gal-13, Gal-14 and Gal-15), which contain one carbohydrate recognition domain (CRD) and may form homodimers; 'tandem repeat-type' galectins (Gal-4, Gal-6, Gal-8, Gal-9 and Gal-12), which contain two distinct CRDs in tandem connected by a linker of up to 70 amino acids and are inherently bivalent; and the unique 'chimera-type' (Gal-3), which consists of unusual tandem repeats of proline-rich and glycine-rich short stretches fused onto the CRD. Following ligand binding, Gal-3 undergoes conformational changes, which enable its oligomerization as pentamers.

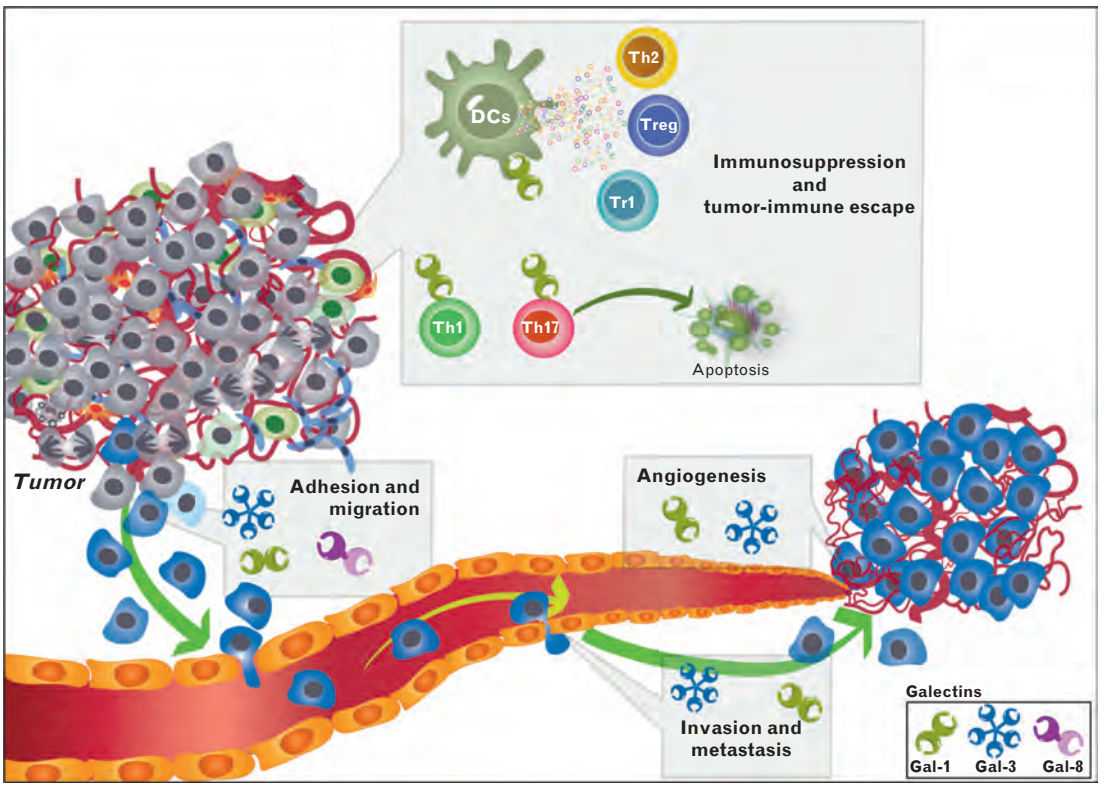

FIGURE 2. Galectins in tumor progression and tumor-associated inflammatory responses. Tumor progression is a multigenic and multistep process involving cell–cell and cell–extracellular matrix (ECM) adhesion, cell invasion and migration, angiogenesis, and escape from immune surveillance. Galectins (Gals) may play key roles at different steps of these processes. Some members can mediate tumor cell adhesion, including adhesion to ECM glycoproteins, as well as homotypic cell adhesion, but can also inhibit adhesion, which could result in tumor cell detachment. The overall effect can be either promotion or inhibition of metastasis. Gal-1, Gal-3 and Gal-8 can influence tumor cell migration and invasion by engaging integrins or other cell-surface proteins involved in cell migration. Gal-3 can also affect the intrinsic motility of cells by remodeling the cytoskeletal elements associated with cell spreading, that is, microfilaments, through yet unidentified mechanisms. Gal-1, Gal-3 and Gal-8 can promote angiogenesis in several tumor types. Tumor secretion of galectins, particularly Gal-1, can control tumor-associated inflammatory responses through diverse mechanisms including selective apoptosis of Th1 and Th17 cells, induction of tolerogenic dendritic cells (DCs) and expansion of $FoxP3^{+}$ and $FoxP3^{(-)}$ T_{reg} (Tr1) cells.

HEMATOLOGICAL MALIGNANCIES: AN OVERVIEW

Hematological malignancies include numerous forms of acute and chronic lymphoproliferative and myeloproliferative diseases. The first description of such a disease was made by Thomas Hodgkin in 1832, and 33 years later the same disease of lymph nodes and spleen was described by Samuel Wilks, for which he designated the subtitle 'Hodgkin's disease', in recognition of the initial description. Hematological malignancies derive from either of the two major blood cell lineages: myeloid and lymphoid cells. Lymphomas, lymphocytic leukemias and myeloma belong to the lymphoid line, whereas acute and chronic myelogenous leukemia are of myeloid origin. The classification of these pathological entities is highly complex and is based on a combination of features that comprise the morphology of the tumor cells, immunophenotype, genetic abnormalities and clinical features [26]. Some forms are very aggressive, whereas others are so benign that they may only be diagnosed by chance. A critical aspect in hematological malignancies is the dynamic interaction between transformed cells and the microenvironment in bone marrow and lymphoid tissues. Compelling evidence indicates that neoplastic cells can shape the neighboring microenvironment by directly affecting stromal composition or co-opting immune effectors that are active in tissue remodeling [27,28]. Such changes in the microenvironment may eventually favor neoplastic cell survival and influence the clinical course of the disease.

GALECTINS IN HODGKIN'S LYMPHOMA

Classical Hodgkin's lymphoma (cHL) is a B-cell malignancy with approximately 20 000 newly diagnosed patients each year in North America and Europe [29]. This tumor type derives from a preapoptotic germinal center B cell that has undergone crippling mutations of prearranged immunoglobulin genes [30]. Histopathologically, cHL is composed of small numbers of malignant Reed–Sternberg cells within an extensive inflammatory infiltrate that includes abundant Th2 and T_{reg} cells capable of suppressing antitumor responses [31]. Juszczynski *et al.* [15] found that Reed–Sternberg cells selectively overexpress galectin-1 through an activating protein-1 (AP-1)-dependent enhancer. In cocultures of Reed–Sternberg cells and human activated T cells, galectin-1 limited T-cell viability, increased the secretion of Th2-type cytokines and promoted the expansion of $CD4^+CD25^{high}$ $FoxP3^+$ T_{reg} cells [15]. Moreover, this lectin inhibited proliferation and IFN-γ production by Epstein–Barr virus (EBV)-specific $CD8^+$ T cells [32]. Interestingly, the synchronized expression of galectin-1 and an activated AP-1 pathway has been proposed as a diagnostic signature of cHL [33]. Galectin-1 was found to be selectively expressed by malignant Reed–Sternberg cells in more than 90% of primary cHLs and its expression correlated with the activated AP-1 component c-Jun. In contrast, diffuse large B-cell lymphomas (DLBCLs) and primary mediastinal large B-cell lymphomas do not express significant amounts of this lectin. However, anaplastic large cell lymphoma (ALCL), an aggressive T-cell tumor with similar features to cHL, consistently expressed both galectin-1 and activated c-Jun [33]. Yet, ALCL but not cHL cells were themselves sensitive to galectin-1-induced cell death [34]. Moreover, galectin-1 expression was associated with aggressiveness in murine T-cell lymphoma models [35]. Of note, galectin-1 expression not only delineates cHL from other types of lymphoma but also serves as a predictive biomarker for relapsed/refractory disease as demonstrated by proteomic analysis of tissue samples from cHL patients [36▪]. Also, serum levels of galectin-1 were found to be associated with tumor burden and adverse clinical features in a large cohort of cHL patients [37▪].

EBV^+ posttransplant lymphoproliferative disorders (PTLDs) are a heterogenous group of B-cell disorders that range from polyclonal B-cell hyperplasia to monoclonal aggressive B-cell lymphoma [38]. The shared clinical features of cHL and EBV-driven PTLDs and the emerging link between galectin-1 expression and tumor-immune escape prompted the investigation of this lectin in PTLDs. EBV-transformed lymphoblastoid B cell lines and primary PTLDs overexpressed galectin-1 through the mechanisms involving interaction of the latent membrane proteins (LMP)-1 and LMP-2 with AP-1 and phosphatidylinositide 3-kinase (PI3K) signaling. Blockade of galectin-1 using a newly developed neutralizing monoclonal antibody selectively inhibited galectin-1-driven apoptosis of EBV-specific cytotoxic T cells [39▪]. These data emphasize the diagnostic and prognostic values of AP-1-dependent galectin-1 expression and its immunosuppressive activity in cHL and EBV-driven PTLD.

GALECTINS IN NON-HODGKIN'S LYMPHOMA: FOLLICULAR LYMPHOMA AND DIFFUSE LARGE B-CELL LYMPHOMA

Follicular lymphoma is the most frequent non-Hodgkin's disease and is generally associated with an indolent clinical course and good initial response to treatment. However, transformation into the more aggressive DLBCL occurs in 25–60% of cases and is associated with poor clinical outcome [40]. Using a gene array approach, Shipp *et al.* [41] reported that galectin-3 is overexpressed in DLBCL, being one of the best gene transcript discriminators between indolent follicular lymphoma and DLBCL. The high expression of galectin-3 in malignant cells was subsequently observed at the protein level in small cohorts of DLBCL [42] and was recently confirmed in a large cohort of 259 primary samples using a tissue microarray [43▪]. The relevance of galectin-3 in resistance of DLBCL cells to apoptosis was recently addressed [43▪]. The authors found that DLBCL cells express galectin-3 both intracellularly and associated to the cell surface. Given that galectin-3 may have different functions according to its subcellular compartmentalization, the authors used a galectin-3 glycan antagonist, GCS-100, to remove galectin-3 specifically from the DLBCL cell surface. This procedure sensitized DLBCL cells to apoptosis induced by different chemotherapeutic agents through a caspase-8-mediated pathway. By co-immunoprecipitation, the tyrosine phosphatase CD45 was identified as the major receptor for galectin-3 on DLBCL cells. The removal of cell-surface galectin-3 from CD45 enhanced CD45 phosphatase activity which resulted in increased sensitization to cell death. In tumor cells, the antiapoptotic activity of galectin-3 has been mostly attributed to the cytoplasmic fraction, whereas cell-surface-associated galectin-3 has been implicated in the promotion of cell adhesion and metastasis. Thus, cell-surface galectin-3 plays a central role in DLBCL resistance to apoptosis.

There is more limited information on the role of galectin-7 in hematological malignancies [44].

In normal tissues, galectin-7 is found mainly in stratified squamous epithelia, while it is also expressed in certain types of cancer cells such as thyroid tumors. Using an antisense approach, it was found that reduced expression of galectin-7 delayed dissemination and growth of tumor cells in an aggressive model of murine lymphoma. Decreased invasion of lymphoma cells in target organs correlated with a reduced expression of matrix metalloproteinase-9 (MMP-9), an enzyme associated with poor prognosis in non-Hodgkin's lymphomas [44].

GALECTINS IN CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is a clinically heterogeneous disease characterized by the accumulation of clonal B lymphocytes in blood, bone marrow, and lymphoid organs. The progression of CLL strongly depends on signals from the tissue microenvironment that regulate the survival and proliferation of the malignant clone [45]. We have recently investigated the role of galectin-1 in CLL [46▪]. We found that, compared to healthy individuals, CLL patients exhibit higher concentrations of galectin-1 in plasma, with it being particularly elevated in patients with advanced disease (Binet C stage) and poor prognostic markers (CD38 and ZAP-70) [45]. Similarly, an increased expression of galectin-1 was detected in bone marrow biopsies from CLL patients with progressive disease, which correlated with increased numbers of $CD68^+$ cells. To determine whether galectin-1 secreted by myeloid cells can influence leukemic B-cell responses, we differentiated nurse-like cells from monocytes and knocked down galectin-1 in these cells. Silencing galectin-1 in nurse-like cells inhibited the expression of activation markers and the production of key molecules such as IL-10 and CCL3 by leukemic B cells. These findings suggest that myeloid-derived galectin-1 is required for full stimulation of CLL cells. Given the central role of B-cell receptor (BCR) signaling in the survival, proliferation and trafficking of CLL cells, we further evaluated whether galectin-1 can modulate this pathway. We found that galectin-1 decreased the threshold of BCR signaling as assessed by Syk and Erk1/2 phosphorylation induced by suboptimal concentrations of anti-IgM. Collectively, these data suggest that galectin-1 contributes to CLL cell activation and may help to establish the appropriate microenvironment for leukemic progression.

GALECTINS IN CUTANEOUS T-CELL LYMPHOMA

Cutaneous T-cell lymphomas (CTCLs) are a heterogenous group of extranodal non-Hodgkin's lymphomas characterized by the primary accumulation of malignant T cells in the skin [47]. Patients with the two predominant clinical forms of CTCL, called mycosis fungoide and Sézary's syndrome, typically develop severe immunodeficiency during disease progression, and advanced stage patients frequently die of infections and not from the tumor burden. As mycosis fungoide/Sézary's syndrome advances, the clonal dominance of the malignant cells results in the expression of predominantly Th2 cytokines (e.g. IL-4, IL-5 and IL-10) [48]. Interestingly, malignant CTCL cells express high amounts of galectin-1 [49]. However, they are themselves resistant to galectin-1 as they exhibit a glycosylation phenotype characterized by the presence of sialylated core 1 O-glycans [49]. This is in agreement with the glyco-profile of normal Th2 cells in which repertoire of cell-surface glycans dictates resistance to galectin-1-induced death [6]. Interestingly, CTCL cells also influence the differentiation of nonmalignant T cells via secretion of galectin-1. Cedeno-Laurent *et al.* [10▪] found that conditioned media from CTCL cells inhibit normal T-cell proliferation and favor Th2 cytokine secretion. As patients with advanced disease exhibit high plasma levels of galectin-1, this endogenous lectin has been proposed as a key effector used by CTCL cells to blunt antitumor responses and augment susceptibility to opportunistic infections.

GALECTINS IN CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia (CML) is a clonal disorder characterized by the dysregulated production of mature myeloid cells. The constitutive active fusion tyrosine kinase, Bcr-Abl, is responsible for deregulated cell proliferation and resistance to apoptosis of CML cells [50]. CML typically begins with a slow, chronic accumulation and over the course of several years progresses toward an accelerated phase and ultimately to a blast crisis, that clinically resembles an acute leukemia. The expression of galectin-3 in primary leukemic cells from bone marrow samples was studied by Yamamoto-Sugitani *et al.* [51▪]. They found that CML cells in chronic phase were highly positive for galectin-3 compared with bone marrow hematopoietic cells from healthy volunteers or samples from patients with acute leukemia. Of note, co-culture with bone marrow stromal cells induced the expression of galectin-3 in five CML cell lines which conferred resistance to genotoxic agents. Likewise, overexpression of galectin-3 in CML cells increased their proliferative potential, favored chemotactic cell migration and inhibited drug-induced

cytotoxic effects. Using a mouse xenograft model for CML, it was shown that overexpression of galectin-3 in transplanted leukemic cells facilitated their migration and long-term lodgment in the bone marrow.

GALECTINS IN ACUTE MYELOGENOUS LEUKEMIA

Acute myelogenous leukemia (AML) is a malignant disease defined by the rapid growth of abnormal myeloid cells that accumulate in the bone marrow and interfere with the production of normal blood cells [52]. A recent study by Cheng *et al.* [53▪] has evaluated galectin-3 mRNA expression in 280 bone marrow samples from AML patients. The study shows that galectin-3 is an independent poor prognostic factor, irrespective of age, leukocyte counts or karyotype, and might serve as a new biomarker in AML [53▪]. Also, there are a number of studies reporting the role of galectin-9 and its ligand TIM-3 on AML. This type of leukemia is associated with a T-cell exhaustion phenotype that prevents a robust antitumor response and may facilitate AML progression [54]. By using a murine model of AML, Zhou *et al.* [55] explored the role of the galectin-9/TIM-3 axis in T-cell dysregulation. They found that TIM-3 was highly expressed in $CD8^+$ T lymphocytes from mice with advanced AML. These T cells were dysfunctional as they secreted lower levels of IFN-γ and TNF than naive $CD8^+$ T lymphocytes. Galectin-9 from AML cells contributed to the exhaustion phenotype as evidenced in galectin-9-deficient mice challenged with galectin-9^+ AML cells. Administration of a blocking TIM-3 fusion protein has an additive effect with an antibody directed to the inhibitor protein programmed death ligand-1 (PD-L1) for restoring the effector function of exhausted T cells, leading to superior survival of AML-bearing mice. Of note, TIM-3 was highly expressed on most types of human AML cells and their engraftment in mice could be blocked using a specific anti-TIM-3 antibody. Collectively, these data suggest that blockage of the galectin-9/TIM-3 pathway could be an attractive option for AML treatment.

GALECTINS IN MULTIPLE MYELOMA

Multiple myeloma is characterized by the progressive accumulation of plasma cells in the bone marrow. Most cases of multiple myeloma also exhibit high serum levels of the clonal immunoglobulin, known as paraprotein, which can cause renal failure [56]. Two different antagonists of galectin-3 have been tested in multiple myeloma with the aim of interfering with the supporting effect of galectin-3 on malignant cells. One of these inhibitors, GCS-100, is a complex carbohydrate capable of inducing multiple myeloma cell apoptosis through the activation of both the intrinsic and extrinsic pathways [57]. GCS-100 induces cell death even in multiple myeloma clones resistant to dexamethasone, melphalan, doxorubicin or bortezomib, suggesting its potential utility in myeloma therapy. More recently, galectin-3C, the N-terminally truncated form of galectin-3, has been tested in a NOD/SCID mouse model harboring human multiple myeloma [58]. *In vitro*, galectin-3C exhibited modest antiproliferative and antimigratory effects on multiple myeloma cell lines, but acted synergistically with bortezomib to impair chemotaxis toward CXCL12 and induce angiogenesis. Using a xenograft model of human multiple myeloma transplant in NOD/SCID mice, a strong reduction of tumor growth was observed in animals receiving galectin-3C with or without bortezomib, thus justifying their clinical testing in multiple myeloma.

The role of galectin-1 and galectin-9 has also been analyzed in multiple myeloma. Abroun *et al.* [59] found that galectin-1 bound to and induced the aggregation of β1-integrin on CD45RA(−) multiple myeloma cells, leading to phosphorylation of ERK, Akt and IκB proteins. This interaction supported the viability and proliferation of multiple myeloma cells. However, in $CD45RA^+$ multiple myeloma cells, galectin-1 induced growth arrest through inhibition of ERK phosphorylation. In summary, galectin-1 has dual functions on multiple myeloma cell lines depending on the expression of CD45RA.

Finally, a recombinant protease-resistant form of galectin-9 has been shown to exhibit robust antiproliferative effects on multiple myeloma cells [60]. These effects were partially dependent on the activation of the MAPK pathway and were evident even on samples from multiple myeloma patients showing poor-risk factors, such as deletion of 13q.

CONCLUSION

During the last decade, a better understanding of the cellular and molecular mechanisms underlying tumor progression has provided the appropriate framework for the development of therapeutic strategies for cancer immunotherapy. Under this complex scenario, galectins have emerged as promising molecular targets for cancer therapy not only in solid tumors, but also in hematologic malignancies. Galectin inhibitors have the potential to be used as antitumor and antimetastatic agents in those cases in which galectins are upregulated in tumor microenvironments. Here, we discuss the recent literature

on the role of galectins, particularly galectin-1, galectin-3, galectin-7 and galectin-9, in hematologic malignancies (Fig. 3). The emerging data promise a future scenario in which the selective blockade of individual members of the galectin family, either alone or in combination with other therapeutic regimens, will contribute to halt tumor progression by inhibiting tumor cell invasiveness, proliferation, angiogenesis and immune escape.

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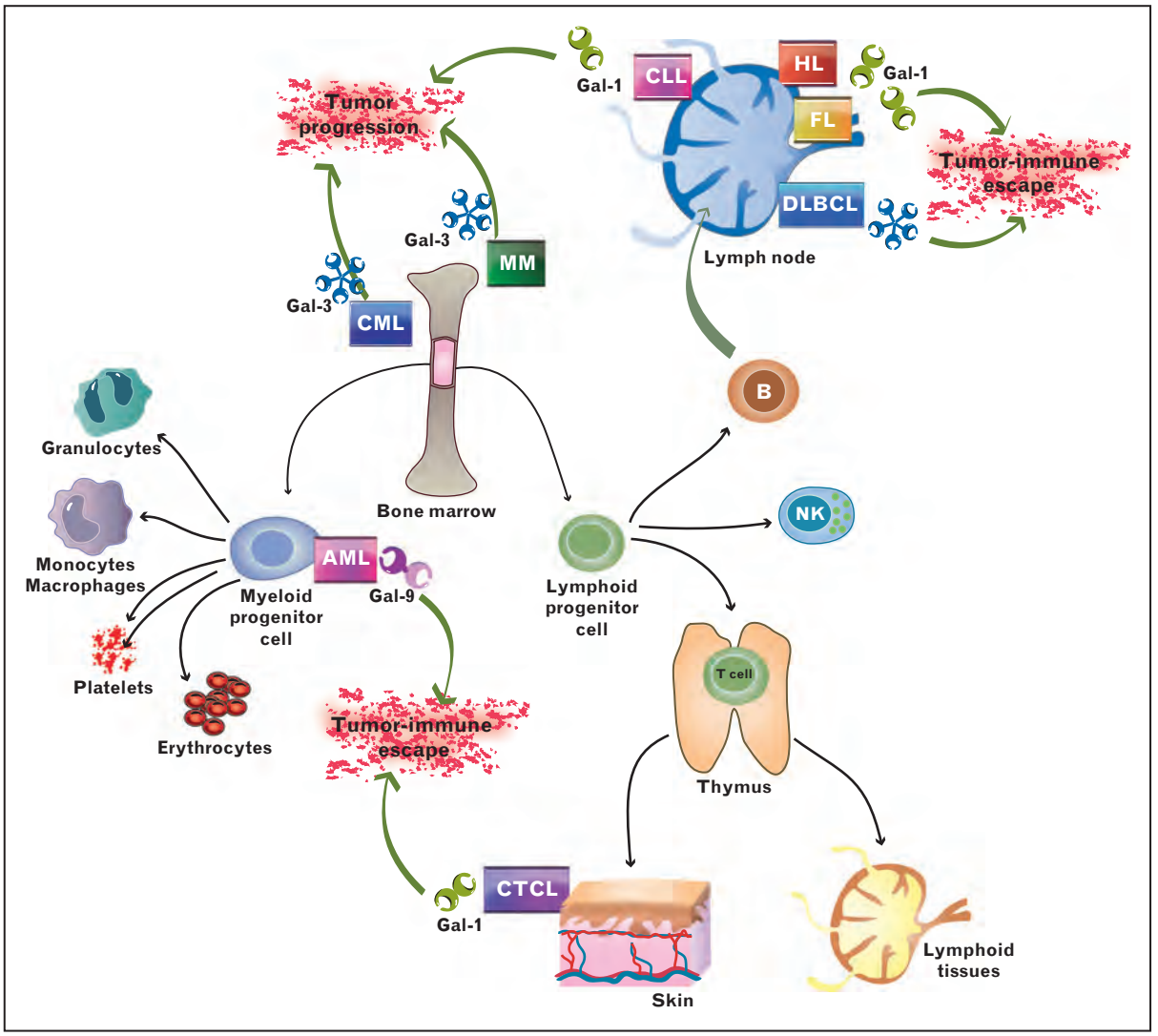

FIGURE 3. Galectins in hematologic malignancies. Circulating leukocytes differentiate from myeloid or lymphoid progenitors in the bone marrow. Malignant transformation can affect the precursor cells within the bone marrow (i.e. AML and CML), mature cells in lymphoid organs (i.e. CLL and FL) or memory lymphocytes in peripheral tissues (i.e. CTCL). Galectins secreted by malignant leukocytes and cells from the microenvironment can control tumor onset and growth at different locations. Gal-3 favors CML and MM progression by facilitating bone marrow homing and access to survival signals. Similarly, Gal-1 from nonmalignant myeloid cells increases the activation and survival of CLL cells in lymphoid tissues. Galectins may also influence the progression of hematologic neoplasms by limiting the magnitude of an effective immune response. Tumor-secreted Gal-1, Gal-3 and Gal-9 activate different tolerogenic circuits that allow tumor-immune escape in HL, FL, DLBCL, CTCL and AML. AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CTCL, cutaneous T-cell lymphomas; DLBCL, diffuse large B-cell lymphomas; FL, follicular lymphoma; HL, Hodgkin's lymphoma; MM, multiple myeloma.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 395).

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