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Review Article

Galectins in hematological malignancies

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Abstract: Carbohydrates are traditionally considered to be an important source of energy for living organisms. In the field of biology, they are defined as organic compounds composed of carbon, hydrogen, and oxygen that are organized into ring structures. The analysis of these structures and their functions has led to a new field of biology called "glycobiology." In the biomedical sciences, glycobiology is rapidly emerging to be an integral part of complex biological processes. Changes in glycan structures and the interactions of these structures with endogenous carbohydrate-binding proteins, known as lectins, are now considered to be potential biomarkers on cancer cells for monitoring tumor progression. Evidence suggesting that the interactions between lectins and their ligands have a major role in the different steps of cancer progression has accumulated at a rapid pace and has gained the attention of several oncologists. This is particularly true for galectin family members because changes in their expression levels correlate with alterations in cancer cell growth, apoptosis, and cell-cell and cell-matrix interactions. Here we provide an integrated view of the role of galectins in hematological malignancies.

Keywords: galectins, lymphoma, apoptosis, gene profiling, immunosuppression

Introduction

Galectins, formerly known as S-type lectins, represent a family of evolutionarily conserved animal lectins that are widely distributed from lower invertebrates to higher vertebrates. They were among the first families of lectins to be identified in animals. They were initially described in the electric eel, *Electrophorus electricus*, as low-molecular-weight, β-galactoside-binding, soluble proteins (electrolectins) [1]. In mammals, the first protein with similar binding properties was purified from calf heart and lung protein extracts and was later named "galectin-1" [2]. Subsequently, several groups identified new members of the galectin family in protein extracts obtained from various tissues by using their ability to bind galactose residues on rabbit erythrocytes and cloning approaches based on sequence homology. In 1994, a joint effort by several investigators in the field led to a new nomenclature in which the term "galectins" was used to define lectins with an affinity for β-galactosides and with sequence similarity in the carbohydrate-binding site [3].

Galectins are numbered according to the order of their discovery. The 15 members of the family are normally classified according to their structure and number of carbohydrate recognition domains (CRDs). The galectins have either one (Galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15) or two (Galectin-4, -6, -8, -9, and -12) CRDs that are linked by a hinge peptide (**Figure 1**). There is also a chimeric form of galectin (i.e. galectin-3) that contains one CRD connected to a non-lectin domain. Typically, CRDs are located at the C-terminal end of the protein and consist of a classic β-sandwich fold of approximately 130 amino acid residues. This β-sandwich fold is conserved in all galectins and includes a glycine, which stabilizes the galectin-carbohydrate interactions [4]. The crystal structures of the galectins with a single CRD, such as galectin-1 and -7, have shown that multiple CRDs are present following dimerization [5-6].

Expression of galectins in normal lymphoid cells

Each member of the galectin family exhibits a specific expression pattern in distinct tissues, and galectin expression is regulated during development. It is generally accepted that galectin-1 is the most ubiquitously expressed

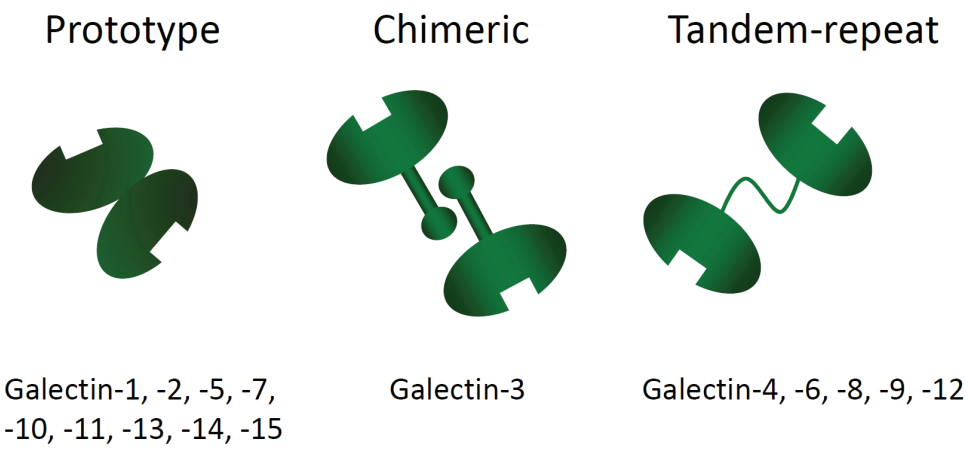

Figure 1. Structures of galectins. Galectins are normally classified on the basis of their structure. Three major groups of galectins are found. The first group consists of the prototypical galectins with one carbohydrate recognition domain [CRD]. The second group contains one memebr, galectin-3, consisting of one CRD covalently linked to a non-carbohydrate domain. Members of the third group harbors two covalently-linked CRD's linked by a small peptide domain [5-50 a.a.]. Prototypical and chimeric galectins can both dimerize, facilitating their binding to multiple carbohydrate chains and stabilize cell surface ligands when secreted in the extracellular space. Additional forms of galectins [e.g. galectin-8 and -9] can also be generated following alternative splicing. Not all galectins are found in human cells. This is the case, for example, for murine galectin-5 and galectin-6 and ovine galectin-11.

member of the family [7]. Galectin-1 is expressed in skeletal, cardiac, ovarian, and adipose tissues as well as in hepatocytes, myofibroblasts, leukocytes, and prostate stromal cells [8-12]. It is also co-expressed with galectin-3 in lymphoid cells, including T and B cells, natural killer (NK) cells, and monocytes/macrophages. However, this conclusion that galectin-1 is the most widely expressed must be considered with caution because most expression studies have focused on galectin-1 and galectin-3. Not surprisingly, the expression patterns and the roles of the other galectin family members remain poorly understood. The accessibility of new public databases containing microarray data and other forms of high-throughput, functional profiling data submitted by the research community may help to address this issue [13]. These data suggest that the different galectin family members are expressed in many tissues, at least at the mRNA level. The expression patterns, however, differ significantly between the different members of the family. For example, galectin-7 expression is mostly restricted to specific epithelial tissues, including the skin and trachea, whereas galectin-15 is mainly found in the cerebral cortex (**Figure 2**). In contrast, galectin-2 expression is predominantly restricted to the gastrointestinal tract [14]. Therefore, it is not surprising that distinct expression patterns were observed for the galectins in different populations of the lymphoid lineage. Galectin-1, for example, is expressed by macrophages and some populations of NK cells, such as uterine decidual NK cells, but not by peripheral NK cells [15, 16]. Galectin-1 is also secreted by activated $CD4^+$ and $CD8^+$ effector T cells, most notably upon antigen recognition [8, 17]. Galectin-3 is expressed in developing myeloid cells, with stronger expression in late mature myeloid cells. In fact, monocyte-macrophages, neutrophils, eosinophils, and particularly basophils and mast cells all express galectin-3 under normal conditions. However, galectin-3 is not expressed in B and T lymphocytes, although it is induced in T cell lines infected with human T-cell lymphotropic virus-I or human immunodeficiency virus [18]. Taken together, these expression profiles support the idea that the members of the galectin family have important roles in lymphoid cell functions and, therefore, could be implicated in lymphoid malignancies.

Galectins in lymphoid neoplasms

Given the expression of galectins in normal lymphocytes, several studies have focused on the expression of galectins in B and T cell lymphomas. Galectin-3, for instance, is expressed at

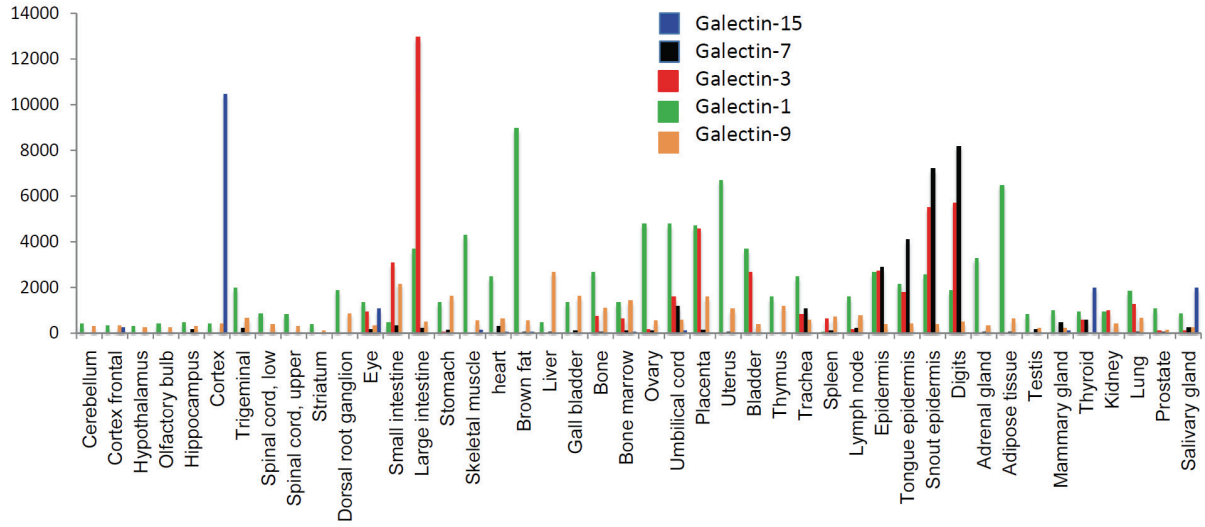

Figure 2. Expression profiles of galectins. Schematic overview of showing mRNA expression profiles of major members of the galectin family. Data were retrieved from the Gene Expression Omnibus [GEO] repository at the National Center for Biotechnology Information [NCBI] archives.

high levels in diffuse large B-cell lymphoma (DLBCL) and multiple myeloma [19-20]. Galectin-7 is also expressed in DLBCL and other types of lymphoma, including follicular lymphoma [21]. The expression of galectin-7 in lymphomas was rather unexpected because normal B and T lymphocytes do not express galectin-7. Subsequent gene expression studies revealed that *de novo* expression of galectin-7 is most likely linked to the hypomethylation of its promoter [22]. Therefore, it is not surprising that *de novo* expression of the galectins was observed in cancer cells despite their absence in normal cells because the expression of the galectin family is controlled, at least in part, by DNA methylation. Whether galectin-3 and galectin-7 have similar roles in DLBCL disease progression is currently unclear, but it is considered likely because both of these galectins have been shown to confer resistance to apoptosis [21, 23-24]. The discovery that galectins are expressed in lymphomas was initially surprising because of the pro-apoptotic role that is generally attributed to galectins. However, a dichotomous role in controlling apoptotic pathways is not unusual for members of the galectin family and has been well documented in the case of galectin-3 [25]. The dual apoptotic role of galectin-3 is possibly linked to its intracellular distribution (nuclear vs. cytoplasmic) [26]. Galectin-3 is observed predominantly in the cytoplasm or the nucleus, depending on the cell type or activation state. Analogous differences in intracellular distribution have also been reported for galectin-7 [27], although there is currently no indication that the dual apoptotic role for galectin-7 is related to its localization. Nevertheless, it is possible that the specific distribution pattern of the galectin could dictate its cellular function through interactions with specific ligands. This hypothesis is supported by studies showing that both galectin-3 and galectin-7 interact with the apoptosis repressor Bcl-2. Furthermore, this hypothesis is supported by data demonstrating that the translocation of galectin-9 from the cytoplasm into the nucleus modulates AP-1 and c/EBP activity in human monocytic cells [28-29]. Such activity is not associated with the extracellular form of galectin-9 [30]. These different localization patterns of the individual members of the galectin family could explain why distinct galectins are found within specific tumor types. This difference has been demonstrated in chronic lymphocytic leukemia (CLL). A significant downregulation of galectin-3, but not galectin-1, has been shown in CLL patients and was most notable in patients with progressive disease compared to normal subjects or patients with an indolent form of CLL [31]. In contrast, galectin-7 expression was significantly increased in CLL patients compared to normal individuals [21]. These observations suggest that monitoring galectin expression may have a prognostic value for CLL.

Role of galectins in regulating the immune response

Historically, the most extensively documented function of galectins is the induction of apoptosis [32-33]. For example, the secreted form of galectin-1 induces apoptosis in different populations of T lymphocytes, including in naive and antigen-primed T lymphocytes [17, 34-36]. It can also sensitize T cells to Fas-mediated cell death [37]. A similar role has been observed in naive and IgM^+ memory B cells [38]. Therefore, the secretion of galectin by tumor cells could have a profound effect on the local immune response by promoting the apoptosis of infiltrating T lymphocytes (see below). The role of galectins in immunity, however, is not limited to the effects on apoptosis. Galectin-1, for example, induces the expression of FcγRI and MHC-II expression on monocytes/macrophages, thereby increasing their ability of these cells to mediate phagocytic functions and antigen presentation [39]. In some B cells, galectin-1 can modulate differentiation and increase antibody production [40]. In fact, pre-B cell survival during development is facilitated by the binding of galectin-1 to integrins, which mediates its interaction with the pre-B cell receptor (BCR) to generate survival signals [41]. The ability of galectins to bind to multiple cell surface receptors and to alter specific signals is a common mechanism used by some galectins to modulate the immune response [40, 42-44]. This is well illustrated by the role of galectin-9 in the interactions between Th1 cells and macrophages. Galectin-9 expression at the surface of *M. tuberculosis*-infected macrophages promotes interactions with Th1 cells via T cell immunoglobulin mucin-3 (TIM-3), membrane glycoproteins that regulate autoimmune and allergic disease. This interaction stimulates bactericidal activity by inducing IL-1β secretion and prevents excessive tissue inflammation by inhibiting the expansion of Th1 cells [45]. These results suggest that the overall balance between the ability of galectins to induce the apoptosis of specific T cell populations and their ability to promote macrophage activation and antigen presentation could determine the overall effect of galectins in cancer.

Carbohydrate-independent functions of galectins

Because galectins are commonly found in the extracellular environment, most studies have focused on the ability of galectins to bind to surface glycoproteins that are expressed on normal or cancer cells. However, there is compelling evidence that galectins might also have non-carbohydrate binding partners, most notably galectins that are found in the cytoplasm or the nucleus. These carbohydrate-independent functions may affect the ability of galectins to mediate the apoptosis of normal and transformed T cells. Indeed, Allione et al. [46] showed that saturating amounts of lactose do not affect the ability of galectin-1 to arrest T cell lymphoma cells in the S and G2M phases of the cell cycle. Similar observations have been made in fibroblasts [47]. In fact, several intracellular carbohydrate-independent binding partners of galectin have been identified, including H-Ras [48-49] and Gemin4, which is a member of a multi-molecular complex that contains at least 15 polypeptides and is involved in the splicing of pre-mRNA [50]. Galectin-7 interacts with Smad3 to regulate its export from the nucleus and, thereby, negatively regulates TGF-β signals [51]. Whether this interaction has a role in hematological malignancies is not yet known, but it is possible because Smad-mediated TGF-β signaling pathways are important in the pathogenesis of many myeloid and lymphoid neoplasms (reviewed in 52). Interestingly, galectin-7 also interacts with Bcl-2 to promote apoptosis in HCT116 and HeLa cells through a lactose-independent mechanism [53]. This observation is reminiscent of the interaction between Bcl-2 and galectin-3 in human BT549 breast cancer cells [54], but the interaction of galectin-3 with Bcl-2 is inhibited by lactose and is associated with a pro-apoptotic function [54]. Interestingly, we have shown that the *de novo* expression of galectin-7 in breast cancer cells is also associated with resistance to apoptosis [24]. Thus, the interactions of galectin-2 and galectin-3 with Bcl -2 result in fundamentally different effects. These different effects could potentially be due to the cellular context of the interaction and/or distinct interacting domains. Given the importance of Bcl-2 in hematological malignancies, these results suggest that the intracellular interactions that involve galectins and members of the Bcl-2 family could be involved in disease progression. The high levels of galectin-7 observed in diffuse-large B cell lymphomas certainly suggest that this is the case [21].

Overall, it is tempting to conclude that the intracellular functions of galectins are mostly independent of their CRDs, whereas their extracellular functions are dependent on their lectin

properties. However, this generalization would not be without its exceptions. Some glycosylated intracellular proteins bind galectins, including cytokeratins and the transcription factor CBP70, both of which have been shown to bind galectin-3 [55-56]. Moreover, the ability of galectins to bind intracellular glycoproteins appears to be important for the trafficking of these glycoproteins to specific intracellular vesicles (reviewed in 57).

Galectins as modulators of the local immune response

Galectins are prime candidates for the modulation of the immune response within the tumor microenvironment because of the critical role that they have in the survival of cells of the lymphoid lineage. Logically, the local secretion of galectins by tumor cells could have significant local immunosuppressive effects by eliminating infiltrating effector T lymphocytes. This process would be significantly relevant to classical Hodgkin's lymphoma (cHL), which is one of the most common subtypes of malignant lymphoma. cHL is characterized by the presence of clonal malignant Hodgkin/Reed-Sternberg (HRS) cells in a tumor microenvironment that is rich in infiltrating cells, including T lymphocytes. The secretion of soluble mediators by the HRS is believed to be the driving force for the abnormal immune response. Interestingly, Juszcynski et al. [58] showed that RS cells and cHL cell lines both secrete large concentrations of galectin-1. Furthermore, the amount secreted is significantly greater than that produced by DLBCL, a type of lymphoma previously known to secrete galectin-1. The authors of this study concluded that the secretion of galectin-1 via the AP-1 pathway in HL decreases the viability of Th1 cells while favoring the activation of Th2 cells, which are known to secrete immunosuppressive cytokines, such as IL-13 (**Figure 3**). Therefore, the new environment favors the emergence and activation of local immunosuppressive $CD4^{+}CD25^{high}FOXP3^{+}$ T regs. The secretion of IL-13 is a common feature of cHL [59-60]. Because IL-13 is known to activate RS cells through STAT6, it is possible that IL-13 activates galectin-1 secretion and, thereby, creates an autocrine immunosuppressive loop. Interestingly, IL-13 and galectin-1 are both downregulated in the therapeutic resolution of inflammation [61], which suggests that these immunosuppressive loops could be a common regulatory process. This hypothesis is further supported by the ability of galectin-1 to reduce the number of Th1 cells and to increase the secretion of Th2-specific cytokines in T cell-mediated autoimmune diseases, such as type 1 diabetes [62]. Moreover, signaling through the IL-13 receptor has been associated with AP-1-dependent gene induction in several cell types [63-65]. This mechanism could explain why a high level of secretion of galectin-1 into the tumor microenvironment correlates with poor survival in cHL; it is also the rationale behind using galectin-1 as a novel biomarker in the prognostic and predictive analysis of cHL.

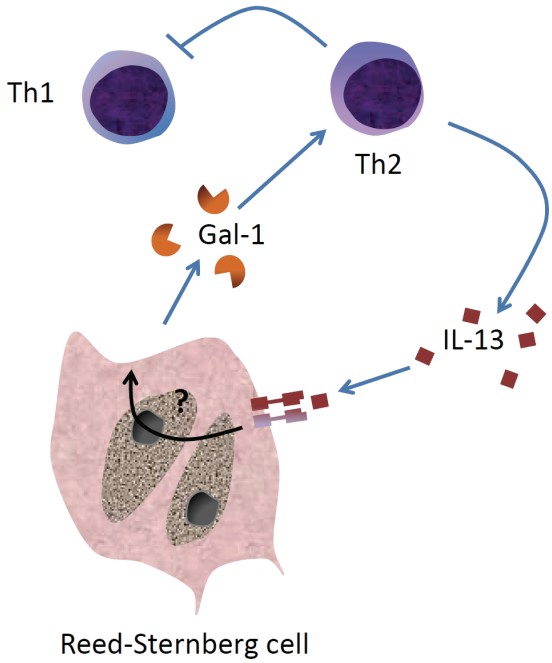

Figure 3. Role of galectin-1 in classical Hodgkin lymphomas. Secretion of galectin-1 by HRS cells favors an immunosuppressive microenvironment by favoring expansion of Th2 cells at the expense of Th1 [58].

Galectin-1 induces apoptosis in T cells by means of specific oligosaccharide structures that are the product of specific glycosyltransferase enzymes, such as the core 2 beta-1,6-N-acetylglucosaminyltransferase (C2GnT) [66]. For example, mouse T cells lacking C2GnT are resistant to galectin-1-induced death [67]. The specific carbohydrate structures are found on critical T cell membrane receptors, such as CD7, which has a central role in the galectin-1-

mediated apoptosis of activated T cells [68-69]. Not surprisingly, CD7-negative cells from Sezary syndrome (SS) patients and the CD7-negative human T cell line, H9, are resistant to galectin-1 -induced death [69]. In contrast, most activated $CD69^+$ $CD7^+$ T cells from patients with T-CLL and T-ALL underwent apoptosis in the presence of galectin-1. This could, at least partially, explain why SS patients have higher numbers of CD7-negative T cells in the peripheral blood compared to healthy donors or patients with other leukemias, even though the T cells of these patients express CD45 and CD43, two receptors that are believed to be ligands for galectin-1. CD7-negative leukemic cells are specifically resistant to galectin-1 because they retain their sensitivity to TNFα- or Fas-mediated apoptosis [69]. It is important to note, however, that the ability of galectin-1 to induce apoptosis in T cells remains somewhat controversial. A recent study showed that while galectin-1, -2, and -4 induce the turnover of phosphatidyl serine in T cells, galectin-1 does not induce apoptosis in activated T cells in the absence of DTT, a reducing agent commonly used to maintain galectin activity [70]. The use of DTT renders cells susceptible to galectin-1-induced cell death [70-72]. Moreover, when a key Cys residue at position 2 is changed to a Ser, the absence of reducing conditions do not affect galectin-1 activity. To add to this controversy, Kovacs-Solyom et al. [73] recently showed that T cells undergo apoptosis when co-cultured with galectin-1-expressing cells but survive when incubated with control cells that do not express galectin-1. Furthermore, the development of a mouse galectin-1 human Ig chimeric molecule that does not require chemical stabilization for Gal-1 ligand recognition has confirmed the ability of galectin-1 to induce apoptosis in activated Th1 and leukemic cells [74].

Galectins as therapeutic targets

The ability of galectins to induce local immunosuppression suggests that galectin-directed therapeutic methods could be a valuable alternative for the treatment of lymphoid malignancies. One example of galectin-targeted therapies is the use of specific antisense RNA oligos to produce a stable inhibition of galectin-1 expression. This strategy has been used to demonstrate that the inhibition of galectin-1 expression results in the reduced adhesion, motility, and invasion of tumor cells in an experimental model of glioblastoma [75-76]. These results are consistent with previous studies that showed that galectin-1 increased the cell motility of cancer cells [77]. At present, no galectin-directed therapeutic strategy has been applied in the treatment of hematological malignancies at the clinical level. However, an antisense strategy to inhibit galectin expression has been used to suppress galectin-7 expression in an experimental model of T lymphoma [21]. Interestingly, the inhibition of galectin-7 in T lymphoma cells using this strategy reduced the ability of these cells to metastasize.

In addition to antisense approaches, several investigators are currently considering the use of natural or synthetic galectin-selective inhibitors that suppress the carbohydrate-binding activity of the galectins. The most common approach thus far has been to use modified citrus pectin (MCP), a water-soluble polysaccharide fiber that is derived from citrus fruit. MCP inhibits gal-3 activity in several types of human cancers, including multiple myeloma (MM) (reviewed by 78). One of these polysaccharides, GCS-100, has been tested in combination with dexamethasone, bortezomib, and PK11195 in clinical trials for the treatment of MM [79]. A recent study showed that the therapeutic efficacy of GCS-100 likely results from multiple physiologic effects. In vitro studies on a panel of human MM cell lines showed that GCS-100 reduced NF-κB activity and the expression of pro-survival proteins, such as Mcl-1 and Bcl-X_L, while increasing apoptosis through both the intrinsic and extrinsic pathways [20]. These effects are consistent with the ability of galectin-3 to induce NF-κB activation [80]. The specific molecular mechanism[s] by which GCS-100 exerts its therapeutic effects remain unclear. An alternative approach to polysaccharides is to use low-molecular-weight glycoamine analogs, which have been shown to be effective in animal models of breast cancer [81]. Other investigators have used wedge-like glycodendrimers, a family of synthetic, carbohydrate-functionalized, multivalent molecules that are created by the attachment of multiple lactoside moieties to disubstituted benzoic acid [82]. In recent years, however, a large panel of efficient and stable galectin inhibitors with a relatively high affinity for specific members of the galectin family have been generated. Because natural galectin ligands, such as lactose and N-acetyllactosamine, have a relatively low affinity for

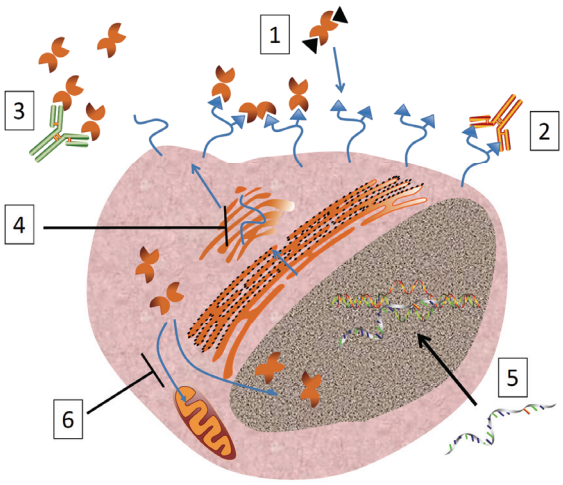

Figure 4. Possible strategies for targeting galectins for therapeutic purposes. A number of ways to block galectin activity or expression have been tested in vitro or in pre-clinical settings. They include [1] small molecular weight inhibitors, [2] neutralizing Abs specific for ligands expressed on cell surface receptors or functional domains of galectins [3], [4] small molecular weight N-glycan processing inhibitors [e.g. swainsonine], [5] antisense or RNAi molecules, as well as pharmacological inhibitors specific for transcription factors, which are aimed at inhibiting galectin expression at the transcripional level, and [6] strategies focusing on proteins involved in intracellular trafficking of galectins [e.g. importin].

galectin, researchers use the data obtained from the three-dimensional structures of galectin:ligand complexes to create new libraries of more effective inhibitors (reviewed in 83).

Conclusion

Reducing galectin expression or suppressing the biological function galectin using selective natural or synthetic inhibitors could be a valuable therapeutic strategy because of the role of galectins in the local induction of apoptosis of T lymphocytes (**Figure 4**). Accordingly, significant efforts by both the academic and private sectors have been dedicated to the development of multiple approaches to inhibit galectin activity, including antisense strategies and the development of natural and synthetic inhibitors. However, because the role of galectins in normal physiological processes remains largely unknown, some caution is warranted. This is particularly true considering that some members of the galectin family have a dual role in apoptosis. The lessons learned from the past with other families of proteins associated with tumor progression should guide our future research. Data demonstrating that members of the galectin family are also associated with protection against pathogens [84-85] suggest that galectins could, in some circumstances, play a critical role in the development of the anti-tumor immunity.

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