54 Aliberti, J.S.S. *et al.* (2001) Modulation of chemokine production and inflammatory responses in IFN-γ and TNF-α receptor p55 deficient mice during *Trypanosoma cruzi* infection. *Am. J. Pathol.* 158, 1433–1440
55 dos Santos, P.V. *et al.* (2001) Prevalence of $CD8^{+}$ αβ T cells in *Trypanosoma cruzi*-elicited myocarditis is associated with acquisition of $CD62L^{Low}LFA\text{-}1^{High}VLA\text{-}4^{High}$ activation phenotype and expression of IFN-γ-inducible adhesion and chemoattractant molecules. *Microbes Infect.* 3, 971–984
56 Savino, W. *et al.* (1993) Characterization of the extracellular matrix-containing giant perivarcular spaces in NOD mouse thymus. *Diabetes* 42, 134–140
57 Uniyal, S. *et al.* (1998) A comparison in β1 integrin expression during thymocyte maturation in Balb/c and nonobese diabetic (NOD) mice. *The Immunologist* (suppl. 1), 255
58 Relf, K. *et al.* (2002) Balanced responsiveness to chemoattractants from adjacent zones determines B-cell position. *Nature* 416, 94–99
59 Akashi, K. *et al.* (2000) B-cell lymphopoiesis in the thymus. *J. Immunol.* 164, 5221–5226
60 Anderson, G. and Jenkinson, E.J. (2000) Thymus organ cultures and T-cell receptor repertoire development. *Immunology* 100, 405–410
61 Villa-Verde, D.M.S. *et al.* (1995) The thymic nurse-cell complex: an *in vitro* model for extracellular-matrix-mediated intrathymic T-cell migration. *Braz. J. Med. Biol. Res.* 28, 907–912
62 Kelly, K.A. and Scollay, R. (1990) Analysis of recent thymic emigrants with subset- and maturity-related markers. *Int. Immunol.* 2, 419–425
63 Hazenberg, M.D. *et al.* (2001) T-cell receptor excision circles as markers for recent thymic emigrants: basic aspects, technical approach and guidelines for interpretation. *J. Mol. Med.* 79, 631–640

# Galectins and their ligands: amplifiers, silencers or tuners of the inflammatory response?

**Gabriel A. Rabinovich, Linda G. Baum, Nicola Tinari, Roberto Paganelli, Clara Natoli, Fu-Tong Liu and Stefano Iacobelli**

**Recent evidence has implicated galectins and their ligands as master regulators of immune cell homeostasis. Whereas some members of this family, such as galectin-3, behave as amplifiers of the inflammatory cascade, others, such as galectin-1, trigger homeostatic signals to shut off T-cell effector functions. These carbohydrate-binding proteins, identified by shared consensus amino acid sequences and affinity for β-galactoside-containing sugars, participate in the homeostasis of the inflammatory response, either by regulating cell survival and signaling, influencing cell growth and chemotaxis, interfering with cytokine secretion, mediating cell–cell and cell–matrix interactions or influencing tumor progression and metastasis. The current wealth of new information promises a future scenario in which individual members of the galectin family or their ligands will be used as powerful anti-inflammatory mediators and selective modulators of the immune response.**

Over the past decade, many novel carbohydrate-binding proteins, or lectins, have been documented as playing crucial roles in cell trafficking, signaling and inflammation [1,2]. The role of lectins in inflammatory processes came into focus in the late-1980s, with the identification of selectins and their oligosaccharide ligands as mediators of leukocyte trafficking into injured tissues [1]. Recently, another lectin family, the galectins, has attracted the attention of cell biologists and immunologists as master regulators of immune cell homeostasis and inflammation [2–4].

Galectins are members of a large, growing family of animal lectins that are highly conserved throughout animal evolution [2–4]. They share remarkable sequence similarities in the carbohydrate-recognition domain (CRD), and many family members preferentially recognize galactose-containing saccharide ligands. To date, 14 mammalian galectins have been identified formally in a wide variety of tissues from several species and more are likely to be discovered [2–5]. Based on their biochemical structure, galectins have been classified by Hirabayashi and Kasai into prototype galectins (galectins-1, -2, -5, -7, -10, -11, -13 and -14) [6], which exist as monomers or noncovalent homodimers of a CRD; chimera-type galectins (galectin-3) composed of a nonlectin domain connected to a CRD; and tandem-repeat-type galectins (galectins-4, -6, -8, -9 and -12), consisting of two different CRDs in a single polypeptide chain (Table 1). Although this biochemical classification was first thought to provide a clear-cut definition of each member of the galectin family, recent studies showed that mRNA for the galectin-8 gene encode for six different isoforms [7]. Strikingly, three galectin-8 isoforms belong to the tandem-repeat galectin group, whereas the three others fit into the prototype group.

Some members of the galectin family have also received individual names according to their functions, localization or biochemical properties, including galectin-1 (L-14, bovine heart lectin or galaptin), galectin-3 (Mac-2, L-29, CBP-35 or εBP for 'IgE-binding protein'), galectin-9 (ecalectin),

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**Table 1. Classification of galectins[a]**

| Galectin | Biochemical structure | Localization | Other names | Glycoconjugate ligands |
|---|---|---|---|---|
| 1 | Prototype and monomeric/dimeric | Most organs, lymph nodes, spleen, thymus, placenta, prostate, macrophages, B cells, T cells and dendritic cells tumors | L-14, BHL and galaptin | Matrix glycoproteins: laminin and fibronectin, 90K/Mac-2BP Cell surface receptors: CD45, CD43, CD7, CD2, CD3 and GM1 |
| 2 | Prototype and monomeric/dimeric | Gastrointestinal tract. Tumors | – | |
| 3 | Chimera-type | Mainly in tumor cells, macrophages, epithelial cells, fibroblasts and activated T cells | Mac-2, L-29, CBP-35 and εBP | Matrix glycoproteins: laminin and fibronectin, LAMPS, 90K/Mac-2BP, MP20 and CEA |
| 4 | Tandem repeat-type | Gastrointestinal tract | – | |
| 5 | Prototype | Erythrocytes | – | |
| 6 | Tandem repeat-type | Gastrointestinal tract | – | |
| 7 | Prototype | Skin and tumors of epidermal origin | – | 90K/Mac-2 BP |
| 8 | Tandem repeat-type with novel prototype isoforms | Liver, prostate, kidney, cardiac muscle, lung and brain | – | |
| 9 | Tandem repeat-type | Thymus, T cells, kidney and Hodgkin´s lymphoma | Ecalectin | |
| 10 | Prototype | Eosinophils and basophils | Charcot-Leyden crystal protein | |
| 11 | Prototype and dimeric | Lens | GRIFIN | |
| 12 | Tandem repeat-type | Adipocytes | – | |
| 13 | Prototype | Placenta | PP-13 | |
| 14 | Prototype | Eosinophils | – | |

[a]Abbreviations: CBP35, carbohydrate-binding protein 35kDa; εBP, IgE-binding protein; CEA, carcinoembryonic antigen; GRIFIN, galectin-related interfiber protein; PP13, placental tissue protein 13; BHL, bovine heart lectin.

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galectin-10 (Charcot-Leyden crystal eosinophil protein), galectin-11 (GRIFIN for galectin-related interfiber protein) and galectin-13 (PP-13) [3]. Recently, additional galectin candidates have been identified by screening GenBank databases, not only in mammalian genomes but also in important experimental model organisms, such as *Caenorhabditis elegans*, *Drosophila melanogaster*, zebrafish, and *Arabidopsis thaliana* [2], and even in viruses [2].

Galectins lack a secretion signal peptide required for export by classical vesicle-mediated exocytosis. In general, galectins are synthesized in the cytosol and released from the cell by an unorthodox secretory mechanism that bypasses the endoplasmic reticulum and the Golgi [8,9]. This unusual secretory route might prevent the premature binding of galectins to oligosaccharides on nascent glycoproteins. After release into the extracellular medium, galectins can crosslink β-galactoside-containing cell-surface glycoconjugates, resulting in the modulation of cell signaling, adhesion and cell survival. Although most galectins have been initially defined as soluble proteins confined to cytosolic compartments or released to the extracellular milieu, a new alternative spliced form of galectin-3 has been reported, containing a predicted transmembrane-spanning domain [10].

Although most mammalian galectins bind preferentially to glycoproteins containing the ubiquitous disaccharide *N*-acetyl-lactosamine (Galβ1→4GlcNAcβ1), binding to individual lactosamine units is of relatively low affinity ($Kd \approx 1\ \mu M$), and it is the arrangement of lactosamine disaccharides in repeating chains (polylactosamines) that increases binding avidity. Moreover, detailed structural analysis of the carbohydrate-binding sites suggests subtle differences in carbohydrate-binding specificities of individual members of this family [11]. Whether subtle differences in saccharide specificity might be responsible for distinct biological responses to galectin binding remains a challenging question.

Moreover, it has been suggested that multivalency of individual members of the galectin family and their crosslinking properties might also determine different biological responses [12]. The multivalency of lectins leads to crosslinking and aggregation of specific cell surface glyco-receptors, which, in many cases, are associated with signal transduction events [11,12]. Two types of multivalent complexes have been observed in dimeric galectins. In the first type (type-1), a cross-linked complex occurs between a divalent carbohydrate and a divalent galectin. In the second type (type-2), a cross-linked complex occurs between a carbohydrate and lectin in which the valency of either molecule is greater than two [11]. Therefore, the plasticity of certain galectins, such as galectin-1, to form type-1 or type-2 complexes with glycoconjugates or other supermolecular structures may relate to different biological activities or to opposite effects induced by individual members of this lectin family.

Although most galectins function extracellularly, some intracellular functions have also been postulated, such as the regulation of nuclear pre-mRNA splicing [13], protection from apoptosis [14,15] and induction of apoptosis [16]. In this review, we deal with recent advances in galectin research, focusing on immune cell development, homeostasis and inflammation under physiological and pathological conditions.

### Galectins in T-cell homeostasis and survival

Primary selection of the T-cell repertoire occurs within the thymus, but significant fine-tuning of the repertoire can also occur in the periphery, as a result of preferential expansion or contraction of T-cell populations in response to homeostatic signals. Although the mechanisms regulating T-cell homeostasis and survival are not fully understood, it is well-known that a variety of signals can trigger or block cell death and proliferation.

Galectin-1 has recently emerged as an important contributor to T-cell homeostasis. Galectin-1, a homodimeric prototype galectin, is expressed widely by a variety of cells in central and peripheral immune compartments, including thymic epithelial cells [17], antigen-primed T cells [18], macrophages [19] and activated B cells [20]. Galectin-1 inhibits the proliferation of mitogen-activated T cells and reduces the clonal expansion of antigen-primed $CD8^+$ T cells and human leukemia T cells in a saccharide-dependent manner [18,21,22]. Galectin-1 induces cell-cycle arrest and/or apoptosis of human and murine T cells during development in the thymus and after stimulation in the periphery [23–26]. In the thymus, immature double-positive (DP) thymocytes are most susceptible to galectin-1-induced death. This susceptibility is regulated in part by the developmentally controlled expression of a specific glycosyltransferase, the core 2β-1,6-*N*-acetylglucosaminyltransferase (C2GnT) [27,28]. As the expression of C2GnT is also upregulated after T-cell activation in the periphery, regulated glycosyltransferase expression might control the galectin-1 susceptibility of peripheral T cells as well [28].

Although galectins bind to a relatively ubiquitous disaccharide, lactosamine, different galectins bind preferentially to unique subsets of cell-surface glycoprotein receptors that bear the saccharide ligands. Galectin-1 binds preferentially to CD45, CD43 and CD7 on the surface of thymocytes and T-cell lines, and binding results in clustering of the receptors into unique domains on the cell surface [29–32]. Regarding the functional significance of these counter-receptors, it has been reported that apoptosis of thymocytes and T cells is modulated by CD45 and that CD7 is critical for this process [23,24,30]. However, the precise role of CD43 in galectin-1-induced cell death is still not clear. Because CD7 has been shown to be an essential receptor for galectin-1, the loss of expression of CD7 in some autoimmune diseases and T-cell lymphomas might allow the survival of autoreactive or neoplastic T cells [33].

Galectin-1 binding initiates a variety of signal-transduction events, such as ERK-2 phosphorylation, calcium influx, activation of specific transcription factors (e.g. AP-1) and Bcl-2 downregulation, to influence T-cell physiology and survival [25,26]. Chung *et al.* examined specifically the role of galectin-1 in modulating T-cell receptor (TCR) signaling, and have shown that galectin-1 acts as a partial TCR ligand; galectin-1 antagonizes TCR responses that require costimulation and complete TCR-ζ chain phosphorylation, but permits TCR responses that only require partial signals, such as apoptosis [34].

In addition to the inhibitory role of galectin-1 on T-cell proliferation and survival [19–25], this β-galactoside-binding protein also promotes proliferation of vascular endothelial cells [35]. The seemingly paradoxical positive and negative effects of galectin-1 on cell growth are highly dependent on cell type and cell activation status, and might also be influenced by the relative distribution of monomeric versus dimeric forms [11]. The abundance of proapoptotic galectin-1 in immune privileged sites, such as placenta, brain and reproductive organs [3], suggests that galectin-1 might trigger the death of infiltrating T cells and protect these sites from tissue damage induced by T-cell-derived proinflammatory cytokines.

In contrast to the pro-apoptotic activity of galectin-1 [19–25], galectin-3 has anti-apoptotic activity (Table 2 and Fig. 1). The ectopic expression of galectin-3 in Jurkat cells renders these cells significantly more resistant to apoptosis induced by several stimuli [14]. Moreover, galectin-3-transfected cell lines have higher rates of proliferation compared with control transfectants. Supporting these findings, galectin-3 has been shown to protect human breast carcinoma cells from chemotherapy- and nitric-oxide-induced apoptosis and inhibit cell death induced by loss of cell anchorage (anoikis) [36,37].

In contrast to the extracellular cell death signal triggered by galectin-1, the anti-apoptotic activity of galectin-3 might result from an intracellular function of this chimeric protein [14]. Interestingly, galectin-3 has been shown to rescue cells from apoptosis by interacting with members of the Bcl-2 protein family and protecting against alterations of the mitochondrial membrane [14,38,39]. Furthermore, galectin-3 stimulates DNA synthesis and prevents apoptosis of other cell types, such as human fibroblasts and murine granulocytes [40,41]. Accordingly, peritoneal cells from galectin-3-deficient mice have been reported to undergo accelerated apoptosis after treatment with different apoptotic stimuli [41]. A recent study showed that inhibition of galectin-3 by an antisense strategy also blocked proliferation of TCR-stimulated T lymphocytes [42].

Although lactosamine, the minimal saccharide ligand preferentially recognized by many galectins, is ubiquitous on mammalian N-glycans, repeating units of lactosamine residues (polylactosamine) have higher avidity for galectin binding. These polylactosamine chains can be added to N- or

**Table 2. The galectin family and homeostasis of the immune responses[a]**

| Members of the Galectin family | Apoptosis | Cell adhesion | Inflammation | Cytokine production | Macrophage functions | Chemotaxis | Modulation of autoimmune diseases |
|---|---|---|---|---|---|---|---|
| **Galectin-1** | ↑ Immature thymocytes, activated peripheral T cells and infected macrophages | ↑↓ Opposite effects on different cell types<br>↓ Activated T cells | ↓ Phospholipase-$A_2$-induced edema, neutrophil extravasation and mast cell degranulation | ↓ TNF-α; IL-2 and IFN-γ from activated T cells<br>↓ IL-12 from infected macrophages<br>↑ IL-5 release | ↓ Arachidonic acid release and prostanglandin $E_2$ production | NA | ↓ Ameliorates EAE, CIA, EAMG, Con A-induced hepatitis. Expression in synovial infiltrates |
| **Galectin-3** | ↓ Activated T cells and tumors | ↑ Neutrophil adhesion to laminin and dendritic cell adhesion to naïve lymphocytes | ↑ Mast cell activation, NADPH activation and superoxide production by neutrophils | ↓ IL-5 production from eosinophils and allergen-specific T cells | ↑ Lipopolysaccharide -induced IL-1 production | ↑ Monocytes and macrophages | Increased expression in arthritic synovia. Modulates rat nephrotoxic nephritis |
| **Galectin-7** | ↑ Keratinocytes | NA | NA | NA | NA | NA | NA |
| **Galectin-8** | ↑ Lung carcinoma | Regulates tumor cell adhesion | NA | NA | NA | NA | NA |
| **Galectin-9** | ↑ Immature thymocytes | NA | NA | NA | NA | ↑ Eosinophils | Modulates rat nephrotoxic nephritis induced by anti-basement membrane antibodies |
| **Galectin-12** | ↑ Adypocytes | NA | NA | NA | NA | NA | NA |
| **Galectin-10 and -14** | NA | NA | Both are expressed by eosinophils. Galectin-14 is released after an allergen challenge in an asthma model | NA | NA | NA | NA |

[a]Abbreviations: CIA, collagen-induced arthritis; EAE, experimental autoimmune encephalomyelitis; EAMG, experimental autoimmune myasthenia gravis; IFN-γ, interferon-γ; NA, not available; TNF-α, tumor necrosis factor-α.

O-glycans, and their synthesis is typically controlled by the activity of specific GlcNAc transferases (27,28,43,44]. Although the family of GlcNAc transferases is growing, two GlcNAc transferases have been directly shown to create ligands for galectins. The GnT V enzyme allows elongation of N-linked polylactosamine chains and participates in galectin-3 binding to T cells and control of T-cell signaling. In contrast, the C2 GnT enzyme allows elongation of O-linked polylactosamine chains and participates in galectin-1 binding to T cells and initiation of T-cell death [27,43,44].

Other galectins have also been postulated to play a role in cell-death regulation. The overexpression of galectin-7 on keratinocytes and tumor cell lines increases their susceptibility to ultraviolet B (UVB)- and actinomycin-induced apoptosis [16,45]. Moreover, galectin-9 has been shown to induce the apoptosis of murine thymocytes [46] and more recently, galectin-12, expressed by adipocytes, has been proposed to induce cell-cycle arrest and apoptosis [47]. The role of individual members of the galectin family in the homeostasis of immune responses is shown in Table 2.

### Galectins modulate cell–cell and cell–matrix interactions

In addition to the role of galectins in cell growth and survival, these lectins can potentiate or inhibit cell–cell and cell–matrix interactions (reviewed in Ref. [3]). Galectin-1 and -3 have both pro-adhesive and anti-adhesive properties, regulated by binding of saccharide ligands on cell surface glycoproteins and extracellular matrix (ECM) glycoproteins, such as fibronectin and laminin [48]. For example, galectin-1 expressed by thymic epithelial cells mediates the binding of these cells to T lymphoblastoid cells in a saccharide-dependent manner [17]. By contrast, exogenously added galectin-1, at concentrations below the apoptotic threshold, inhibits interleukin-2 (IL-2)-induced T-cell adhesion to ECM glycoproteins [48].

In contrast, galectin-3 promotes adhesion of neutrophils to laminin [49]. It also mediates adhesion between activated dendritic cells entering the lymph nodes and lymphocytes via L-selectin [50]. Recently, it was shown that phosphorylation of galectin-3 inhibits binding of this lectin to ECM glycoproteins [51], whereas is essential for its anti-apoptotic action [52], suggesting that

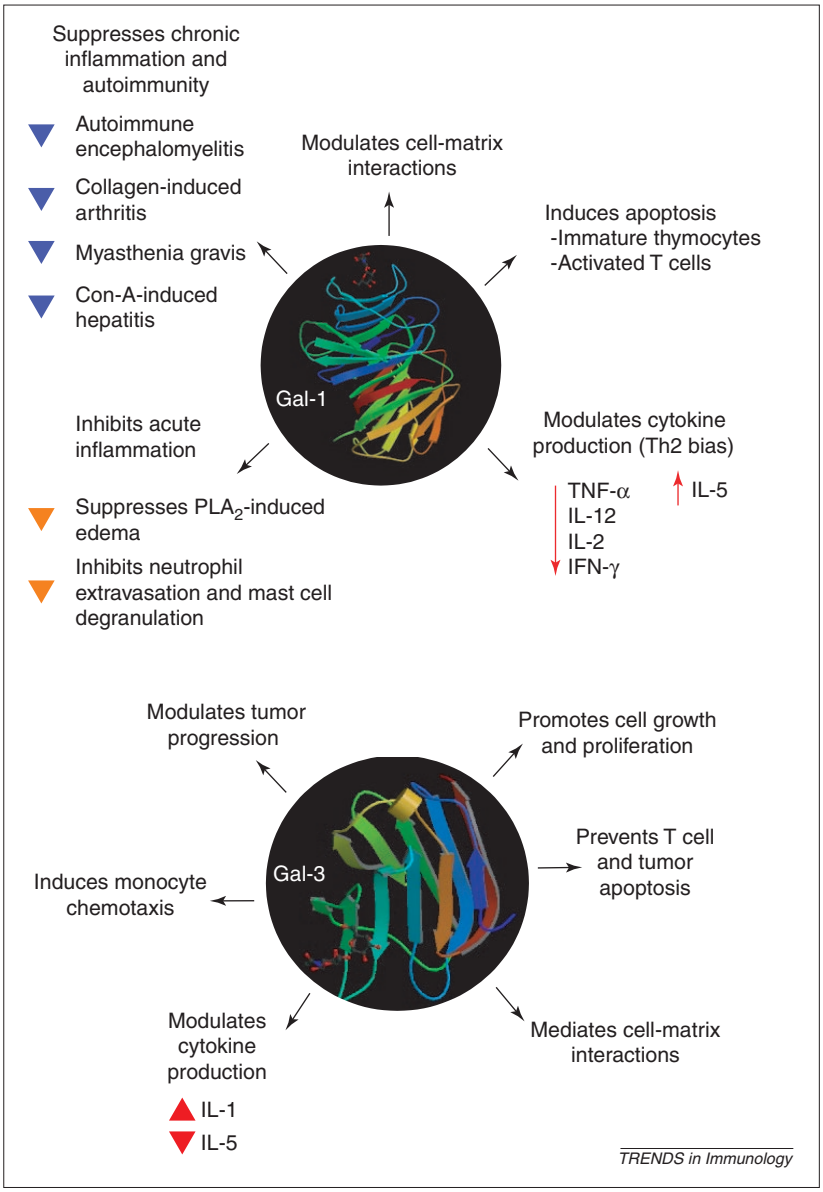


**Fig. 1.** Role of galectins-1 and -3 in different events of the inflammatory response under physiological and pathological conditions. Opposite functions have been assigned for galectins-1 and -3, suggesting that the balance between these two sugar-binding proteins may be crucial for the homeostasis of the inflammatory response.

post-translational modifications could be alternative mechanisms for generating functional diversity among these sugar-binding proteins.

Although the role of other members of the galectin family in cell adhesion and trafficking remains to be elucidated, galectin-8 has recently been shown to form complexes with members of the integrin family to inhibit cell adhesion and extravasation through the ECM [53].

### Galectins in T-cell-mediated immune disorders

Through its ability to inhibit T-cell effector functions, galectin-1 has powerful immunoregulatory effects *in vivo* [54–57]. Offner *et al.* provided clinical and histopathological evidence that galectin-1 prevents the development of experimental autoimmune encephalomyelitis in rats [54]. It has been demonstrated that recombinant galectin-1 and its genetic delivery suppress the inflammatory response in collagen-induced arthritis, an experimental model of rheumatoid arthritis [55]. The injection of fibroblasts genetically engineered to secrete galectin-1 abrogated the clinical and immunological manifestations of arthritis, reduced paw swelling and inhibited production of anticollagen IgG antibodies in DBA/1 mice. This therapeutic effect was accompanied by a shift to a T helper 2 (Th2)-polarized immune response, with decreased interferon-γ (IFN-γ) and increased IL-5 production by lymph node cells from galectin-1-treated mice [55]. The effects of galectin-1 might be related to its proapoptotic activity, because lymph node cells from treated mice were found to be more susceptible to antigen-induced apoptosis [55]. In this context, decreased galectin-1 and increased galectin-3 expression correlated with defective T-cell apoptosis in patients with juvenile rheumatoid arthritis [58].

This anti-inflammatory outcome has also been observed in concanavalin A (Con-A)-induced hepatitis, a T-cell-dependent model of liver injury [57]. Galectin-1 pretreatment was able to prevent both liver injury and T-cell liver infiltration induced by Con A, which was accompanied by the inhibition of tumor necrosis factor-α (TNF-α) and IFN-γ production. Galectins might also have a direct or indirect effect on the production of autoantibodies, because a galectin purified from the electric eel prevented the development of experimental myasthenia gravis, an antibody-mediated autoimmune disorder, in a rabbit model [56]. Moreover, the therapeutic efficacy of galectins-1, -3 and -9 has been tested recently in an experimental model of nephrotoxic nephritis induced by antiglomerular basement membrane antibodies [59]. It should be highlighted that autoimmunity has not been reported in either galectin-1 or galectin-3 knockout mice, suggesting that additional members of this family or other immunoregulatory molecules could potentially compensate for the absence of these proteins [60].

Galectin-3 was first defined as an IgE-binding protein (εBP), suggesting its potential role in allergic inflammation (reviewed in Ref. [4]). Accordingly, recent findings have revealed that galectin-3 specifically inhibits IL-5, but not IL-4, transcription in human eosinophils and allergen-specific T-cell lines [61]. This observation suggests that galectin-3 might be relevant in the context of Th2-mediated immune responses, in contrast to the anti-inflammatory role of galectin-1 in Th1-mediated disorders [55,57]. The finding that galectin-3 inhibits IL-5 production suggests that this lectin can inhibit allergic reactions, whereas galectin-3 is generally considered to be a proinflammatory protein. This issue requires further consideration. In the context of allergic responses, galectin-9 has been reported to be a potent eosinophil chemoattractant [62] and galectins-10 and -14 are

selectively expressed in eosinophils, suggesting their involvement in allergic processes [5,63]. Galectin-14 has been shown to be released after an allergenic challenge in an experimental model of bronchial asthma [5].

Demetriou and colleagues have recently provided indirect evidence of the role of galectins in the regulation of T-cell homeostasis *in vivo* [43]. The authors showed that null mutations in the gene encoding β1,6 *N*-acetylglucosaminyltransferase V (*Mgat 5*), a key enzyme in the *N*-glycosylation pathway, result in increased susceptibility to autoimmune disease and enhanced delayed-type hypersensitivity (DTH) responses. According to their proposed model, galectin-3 forms a multivalent lattice with glycoproteins of the TCR–CD3 complex and thereby restrains lateral mobility of the TCR complex. In the absence of *Mgat 5*, dysregulation of galectin-glycoprotein lattice formation reduces the threshold for TCR-mediated activation [43]. Although the link between T-cell proliferation and autoimmunity in *Mgat 5*$^{-/-}$ mice is intriguing, a direct involvement of galectins *in vivo* during these processes is still to be demonstrated. In line with previous experimental evidence, it might also be possible that the absence of *N*-acetyllactosamine residues on cell-surface glycoproteins of *Mgat-5* null mice might render autoreactive T cells resistant to the proapoptotic effect of galectin-1 or other members of the galectin family [55,57].

### Galectins in acute inflammation

In addition to the role of galectins in chronic inflammation, galectins also participate in acute and allergic inflammation (reviewed in Ref. [4]). Galectin-1 ameliorates edema induced by bee venom phospholipase A2, when pre- or co-injected together with the enzyme [64]. Moreover, it inhibits the release of arachidonic acid from lipopolysaccharide (LPS)-stimulated macrophages, neutrophil extravasation and mast-cell degranulation [64].

In contrast to the anti-inflammatory effects of galectin-1, galectin-3 has been proposed to be a powerful pro-inflammatory signal. It has been reported to activate NADPH oxidase [65], stimulate superoxide production from neutrophils [66], potentiate LPS-induced IL-1 production and promote monocyte chemotaxis [67,68]. Studies of galectin-3 knockout mice have provided significant support for the pro-inflammatory role of this lectin [41,69]. After intraperitoneal challenge, galectin-3-deficient mice had fewer inflammatory cells, with reduced levels of NFkB activation [41].

Galectin-3 has been reported to interact with bacterial LPS *in vitro*, although the functional relevance of this interaction remains to be clarified [70]. It is probable that other molecules contribute to the interaction between galectin-3 and LPS. Of special interest is the galectin-3 ligand, 90K/Mac-2 BP, a serum glycoprotein with immune-regulatory and cell-adhesive functions, which binds CD14 in a LPS-dependent fashion [71].

### Galectins in microbial infections

Recent studies have shown that galectin-1 influences the ability of macrophages to control intracellular infections, either by inhibiting microbicidal activity, promoting parasite replication or inducing host-cell apoptosis [72]. Low concentrations of galectin-1 almost completely block IL-12, but not IL-10, production by *Trypanosoma cruzi*-infected murine-infected macrophages. Selective inhibition of production of this cytokine is reflected by the enhanced survival and replication of intracellular parasites in cultured macrophages, because IL-12 is necessary to induce nitric-oxide-mediated parasite killing. Moreover, high concentrations of this protein trigger the apoptosis of *T. cruzi*-infected, but not normal, murine macrophages [72]. Interestingly, the expression of galectins-1 and -3 is upregulated markedly after parasite or virus infection [72–74].

Galectins and their ligands might play an important role in host–pathogen interactions. Fornarini *et al*. have recently provided evidence of the role of galectin-3 ligand, 90K/Mac-2 BP, in protection of the neonate against acute respiratory infections (ARI) [75]. The authors showed that infants fed with breast milk containing high levels of 90K/Mac-2 BP suffered from ARI less frequently than infants consuming milk with low levels.

### Galectins in tumor progression and metastasis

Galectins have been shown to be involved in many cellular functions that are crucial during cancer progression and metastasis (reviewed in Refs [76,77]). For example, both galectin-1 and -3 have been reported to induce the homotypic adhesion of isolated tumor cells by interacting with soluble or membrane-associated ligands [78–80]. As the survival of blood-borne cancer cells is enhanced by their homotypic adhesion, it is probable that galectin-mediated aggregation of malignant cells favors their homing to secondary sites. Moreover, the involvement of galectins in cell–matrix adhesion, resistance to apoptosis and angiogenesis has been reported [77].

A correlation has been established between galectin expression in the tumor tissues and disease progression in human and murine breast tumors, head and neck cancers, prostate carcinomas, thyroid cancers, colon carcinoma, skin cancer, ovarian carcinomas and astrocytomas [76,77,81]. Moreover, an aberrant increase in the circulating levels of galectin-3 has been reported to be associated significantly with the presence of distant metastasis [82].

Although work to date has focused on galectins-1 and -3, the contribution of other galectins to the metastatic process has been suggested recently [81]. In particular, galectin-8 has been proposed to

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function as a matricellular modulator [53] and galectin-7 has been reported to be an early transcriptional target of the tumor suppressor gene p53 [45]. Further studies are necessary to establish the precise role of each galectin in the tumorigenic and metastatic process.

## Concluding remarks

The current wealth of new information on the galectin family and their ligands promises a ripe field that will reveal novel mechanisms to control basic cellular processes, such as proliferation, signal transduction and cell death, as well as interesting new possibilities in the diagnosis and treatment of disease in the near future. The study of glycan biosynthesis and glycosylation of cell surface receptors in the course of immunological responses may also help us to understand the multifaceted roles of these sugar-binding proteins [44]. This information will contribute to delineate novel therapeutic strategies in autoimmune, inflammatory, allergic and neoplastic processes.

## References


1 Rossiter, H. *et al.* (1997) Selectins, T-cell rolling and inflammation. *Mol. Med. Today* 3, 214–222
2 Cooper, D.N.W. and Barondes, S.H. (1999) God must love galectins; he made so many of them. *Glycobiology* 9, 919–984
3 Rabinovich, G.A. (1999) Galectins: an evolutionarily conserved family of animal lectins with multifunctional properties; a trip from the gene to clinical therapy. *Cell Death Differ.* 6, 711–721
4 Liu, F-T. (2000) Galectins: a new family of regulators of inflammation. *Clin. Immunol.* 97, 79–88
5 Dunphy, J.L. *et al.* (2002) Isolation and characterization of a novel eosinophil-specific galectin released into the lungs in response to allergen challenge. *J. Biol. Chem.* Feb 11 [epub ahead of print]
6 Hirabayashi, J. and Kasai, K. (1993) The family of metazoan metal-independent β-galactoside-binding lectins: structure, function and molecular evolution. *Glycobiology* 3, 297–304
7 Bidon, N. *et al.* (2001) Galectin-8: a complex sub-family of galectins. *Int. J. Mol. Med.* 8, 245–250
8 Cooper, D.N.W. (1997) Galectin-1: secretion and modulation of cell interactions with laminin. *Trends Glycosci. Glycotechnol.* 9, 57–67
9 Mehul, B. and Hughes, R.C. (1997) Plasma membrane targetting, vesicular budding and release of galectin-3 from the cytoplasm of mammalian cells during secretion. *J. Cell Sci.* 110, 1169–1178
10 Gorski, J.P. *et al.* (2002) New alternatively spliced form of galectin-3, a member of beta-galactoside-binding animal lectin family, contains predicted transmembrane spanning domain and leucine zipper motif. *J. Biol. Chem.* [epub ahead of print]
11 Cho, M. and Cummings, R.D. (1997) Galectin-1: oligomeric structure and interactions with polylactosamine. *Trends Glycosci. Glycotechnol.* 9, 47–56
12 Sacchettini, J.C. *et al.* (2001) Multivalent protein–carbohydrate interactions. A new paradigm for supermolecular assembly and signal transduction. *Biochemistry* 40, 3009–3015
13 Dagher, S.F. *et al.* (1995) Identification of galectin-3 as a factor in pre-mRNA splicing. *Proc. Natl. Acad. Sci. U. S. A.* 92, 1213–1217
14 Yang, R.Y. *et al.* (1996) Expression of galectin-3 modulates T-cell growth and apoptosis. *Proc. Natl. Acad. Sci. U. S. A.* 93, 6737–6742
15 Yu, F. *et al.* (2002) Galectin-3 translocates to the perinuclear membranes and inhibits cytochrome c release from mitochondria: a role for synexin in galectin-3 translocation. *J. Biol. Chem.* Feb 11 [epub ahead of print]
16 Kuwabara, I. *et al.* (2002) Galectin-7 (PIG1) exhibits pro-apoptotic function through JNK activation and mitochondrial cytochrome c release. *J. Biol. Chem.* 277, 3487–3497
17 Baum, L.G. *et al.* (1995) Human thymic epithelial cells express an endogenous lectin, galectin-1, which binds to core 2 O-glycans on thymocytes and T lymphoblastoid cells. *J. Exp. Med.* 181, 877–887
18 Blaser, C. *et al.* (1998) β-galactoside-binding protein secreted by activated T cells inhibits antigen-induced proliferation of T cells. *Eur. J. Immunol.* 28, 2311–2319
19 Rabinovich, G.A. *et al.* (1998) Activated rat macrophages produce a galectin-1-like protein that induces apoptosis of T cells: biochemical and functional characterization. *J. Immunol.* 160, 4831–4840
20 Zuñiga, E.I. *et al.* (2001) Regulated expression of galectin-1 during B-cell activation and implications for T-cell apoptosis. *J. Leukoyte Biol.* 70, 73–79
21 Rabinovich, G.A. *et al.* (1997) Specific inhibition of lymphocyte proliferation and induction of apoptosis by CLL-I, a β-galactoside-binding lectin. *J. Biochem.* 122, 365–373
22 Novelli, F. *et al.* (1999) Negative cell cycle control of human T cells by β-galactoside-binding protein (β GBP): induction of programmed cell death in leukaemia cells. *J. Cell. Physiol.* 178, 102–108
23 Perillo, N.L. *et al.* (1997) Galectin-1, an endogenous lectin produced by thymic epithelial cells, induces apoptosis of human thymocytes. *J. Exp. Med.* 97, 1851–1858
24 Perillo, N.L. *et al.* (1995) Apoptosis of T cells mediated by galectin-1. *Nature* 378, 736–739
25 Vespa, G.N. *et al.* (1999) Galectin-1 specifically modulates TCR signals to enhance TCR apoptosis but inhibit IL-2 production and proliferation. *J. Immunol.* 162, 799–806
26 Rabinovich, G.A. *et al.* (2000) Molecular mechanisms implicated in galectin-1-induced apoptosis: activation of the AP-1 transcription factor and downregulation of Bcl-2. *Cell Death Differ.* 7, 747–753
27 Galvan, M. *et al.* (2000) Expression of a specific glycosyltransferase enzyme regulates T-cell death mediated by galectin-1. *J. Biol. Chem.* 275, 16730–16737
28 Nguyen, J.T. *et al.* (2001) CD45 modulates galectin-1-induced T-cell death: regulation by expression of core 2 O-glycans. *J. Immunol.* 167, 5697–5707
29 Pace, K.E. *et al.* (1999) Restricted receptor segregation into membrane microdomains occurs on human T cells during apoptosis induced by galectin-1. *J. Immunol.* 163, 3801–3811
30 Pace, K.E. *et al.* (2000) CD7, delivers a pro-apoptotic signal during galectin-1-induced T-cell death. *J. Immunol.* 165, 2331–2334
31 Fouillit, M. *et al.* (2000) Regulation of CD45-signaling by galectin-1 in Burkitt lymphoma B cells. *Glycobiology* 10, 413–419
32 Walzel, H. *et al.* (2000) Involvement of CD2 and CD3 in galectin-1-induced signaling in human Jurkat T cells. *Glycobiology* 10, 131–140
33 Gabius, H.J. (2001) Probing the cons and pros of lectin-induced immunomodulation: case studies for the mistletoe lectin and galectin-1. *Biochimie* 83, 1–8
34 Chung, C.D. *et al.* (2000) Galectin-1 induces partial TCR ζ-chain phosphorylation and antagonizes processive TCR signal transduction. *J. Immunol.* 165, 3722–3729
35 Sanford, G.L. and Harris-Hooker, S. (1990) Stimulation of vascular cell proliferation by β-galactoside-binding lectins. *FASEB J.* 4, 2912–2918
36 Kim, H.R.C. *et al.* (1999) Cell cycle arrest and inhibition of anoikis by galectin-3 in human breast epithelial cells. *Cancer Res.* 59, 4148–4154
37 Moon, B.K. *et al.* (2001) Galectin-3 protects human breast carcinoma cells against nitric-oxide-induced apoptosis: implication of galectin-3 function during metastasis. *Am. J. Pathol.* 159, 1055–1060
38 Akahani, S. *et al.* (1997) Galectin-3, anti-apoptotic molecule with a functional BH1 (NWGR) domain of Bcl-2 family. *Cancer Res.* 57, 5272–5276
39 Matarrese, P. *et al.* (2000) Galectin-3 overexpression protects from cell damage and death by influencing mitochondrial homeostasis. *FEBS Lett.* 473, 311–315
40 Inohara, H. *et al.* (1998) Galectin-3 stimulates cell proliferation. *Exp. Cell Res.* 245, 294–302
41 Hsu, D.K. *et al.* (2000) Targeted disruption of the galectin-3 gene results in attenuated peritoneal inflammatory responses. *Am. J. Pathol.* 156, 1073–1083
42 Joo, H.G. *et al.* (2001) Expression and function of galectin-3, a beta-galactoside-binding protein in activated T lymphocytes. *J. Leukocyte Biol.* 69, 555–564
43 Demetriou, N. *et al.* (2001) Negative regulation of T-cell activation and autoimmunity by *Mgat5* *N*-glycosylation. *Nature* 409, 733–739
44 Lowe, J.B. (2001) Glycosylation, immunity and autoimmunity. *Cell* 104, 809–812
45 Bernerd, F. *et al.* (1999) Galectin-7 overexpression is associated with the apoptotic process in UVB-induced sunburn keratinotyes. *Proc. Natl. Acad. Sci. U. S. A.* 96, 11329–11334
46 Wada, J. *et al.* (1997) Developmental regulated expression and apoptotic potential of galectin-9, a β-galactoside-binding lectin. *J. Clin. Invest.* 99, 2452–2461
47 Yang, R.Y. *et al.* (2001) Cell cycle regulation by galectin-12, a new member of the galectin superfamily. *J. Biol. Chem.* 276, 20252–20260

48 Rabinovich, G.A. *et al.* (1999) Specific inhibition of T-cell adhesion to extracellular matrix and pro-inflammatory cytokine secretion by human recombinant galectin-1. *Immunology* 97, 100–106
49 Kuwabara, I. and Liu, F-T. (1996) Galectin-3 promotes adhesion of human neutrophils to laminin. *J. Immunol.* 156, 3939–3944
50 Swarte, V.V. *et al.* (1998) Lymphocyte triggering via L-selectin leads to enhanced galectin-3-mediated binding to dendritic cells. *Eur. J. Immunol.* 28, 2846–2871
51 Hadari, Y.R. *et al.* (2000) Galectin-8 binding to integrins inhibits cell adhesion and induces apoptosis. *J. Cell Sci.* 113, 2385–2397
52 Mazurek, N. *et al.* (2000) Phosphorylation of the beta-galactoside-binding protein galectin-3 modulates binding to its ligands. *J. Biol. Chem.* 275, 36311–36315
53 Yoshii, T. *et al.* (2002) Galectin-3 phosphorylation is required for its anti-apoptotic function and cell cycle arrest. *J. Biol. Chem.* 277, 6852–6857
54 Offner, H. *et al.* (1990) Recombinant human β-galactoside-binding lectin suppresses clinical and histological signs of experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* 28, 177–184
55 Rabinovich, G.A. *et al.* (1999) Recombinant galectin-1 and its genetic delivery suppress collagen-induced arthritis via T-cell apoptosis. *J. Exp. Med.* 190, 385–397
56 Levy, G. *et al.* (1983) Prevention and therapy with electrolectin of experimental autoimmune myasthenia gravis in rabbits. *Eur. J. Immunol.* 13, 500–507
57 Santucci, L. *et al.* (2000) Galectin-1 exerts immunomodulatory and protective effects on concanavalin-A-induced hepatitis in mice. *Hepatology* 31, 399–406
58 Harjacek, M. *et al.* (2001) Expression of galectins-1 and -3 correlates with defective mononuclear cell apoptosis in patients with juvenile rheumatoid arthritis. *J. Rheumatol.* 28, 1914–1922
59 Tuchiyama, Y. *et al.* (1999) Efficacy of galectins in the amelioration of nephrotoxic serum nephritis in Wistar Kyoto rats. *Kidney Int.* 58, 1941–1952
60 Poirier, F. and Robertson, E.J. (1993) Normal development of mice carrying a null mutation in the gene encoding the L-14 S-type lectin. *Development* 119, 1229–1236
61 Cortegano, I. *et al.* (1998) Galectin-3 down-regulates IL-5 gene expression on different cell types. *J. Immunol.* 161, 385–389
62 Matsumoto, R. *et al.* (1998) Human ecalectin, a variant of human galectin-9, is a novel eosinophil chemoattractant produced by T lymphocytes. *J. Biol. Chem.* 273, 16976–16984
63 Ackerman, S.J. *et al.* (1993) Molecular cloning and characterization of human eosinophil Charcot-Leyden crystal protein (lysophospholipase). Similarities to the Ig E binding protein and the S-type animal lectin superfamily. *J. Immunol.* 150, 456–468
64 Rabinovich, G.A. *et al.* (2000) Evidence of a role for galectin-1 in acute inflammation. *Eur. J. Immunol.* 30, 1331–1339
65 Karlsson, A. *et al.* (1998) Galectin-3 activates the NADPH oxidase in exudated but not peripheral-blood neutrophils. *Blood* 91, 3430–3438
66 Yamaoka, A. *et al.* (1995) A human lectin, galectin-3 (ε-BP/Mac-2) stimulates superoxide production by neutrophils. *J. Immunol.* 154, 3479–3487
67 Jeng, K.C.G. *et al.* (1994) An endogenous lectin, galectin-3 (ε-BP/Mac-2) potentiates IL-1 production by human monocytes. *Immunol. Lett.* 42, 113–116
68 Sano, H. *et al.* (2000) Human galectin-3 is a novel chemoattractant for monocytes and macrophages. *J. Immunol.* 165, 2156–2164
69 Colnot, C. *et al.* (1998) Maintenance of granulocyte numbers during acute peritonitis is defective in galectin-3-null mutant mice. *Immunology* 94, 290–296
70 Mey, A. *et al.* (1996) The animal lectin galectin-3 interacts with bacterial lipopolysaccharides via two independent sites. *J. Immunol.* 156, 1572–1577
71 Yu, B. and Wright, S.D. (1995) LPS-dependent interaction of Mac-2-binding protein with immobilized CD14. *J. Inflamm.* 45, 115–125
72 Zuñiga, E.I. *et al.* (2001) Regulated expression and effect of galectin-1 on *Trypanosoma-cruzi*-infected macrophages: modulation of microbicidal activity and survival. *Infect. Immun.* 69, 6804–6812
73 Giordanengo, L. *et al.* (2001) Anti-galectin-1 autoantibodies in human *Trypanosoma cruzi* infection: differential expression of this β-galactoside-binding protein in cardiac Chagas' disease. *Clin. Exp. Immunol.* 124, 266–273
74 Hsu, D.K. *et al.* (1996) Human T lymphotropic virus-I infection of human T lymphocytes induces expression of the β-galactoside-binding lectin, galectin-3. *Am. J. Pathol.* 148, 1661–1670
75 Fornarini, B. *et al.* (1999) Human milk 90K (Mac-2 BP): possible protective effects against acute respiratory infections. *Clin. Exp. Immunol.* 115, 91–94
76 Nangia-Makker, P. *et al.* (2000) The role of galectin-3 in tumor metastasis. In *Lectins and Pathology* (Caron, M. and Seve, A-P., eds), pp. 67–77, Harwood Academic Publishers
77 Van den Brule, F.A. and Castronovo, V. (1999) Laminin-binding lectins during invasion and metastasis. In *Lectins and Pathology* (Caron, M. and Seve, A-P., eds) pp. 79–121, Harwood Academic Publishers
78 Inohara, H. *et al.* (1996) Interactions between galectin-3 and Mac-2-binding protein mediate cell–cell adhesion. *Cancer Res.* 56, 4530–4534
79 Tinari, N. *et al.* (2001) Glycoprotein 90K/MAC-2BP interacts with galectin-1 and mediates galectin-1-induced cell aggregation. *Int. J. Cancer* 91, 167–172
80 Glinsky, V.V. *et al.* (2000) Effects of Thomsen-Friedenreich antigen-specific peptide P-30 on β-galactoside-mediated homotypic aggregation and adhesion to the endothelium of MDA-MB-435 human breast carcinoma cells. *Cancer Res.* 60, 2584–2588
81 Lahm, H. *et al.* (2001) Comprehensive galectin fingerprinting in a panel of 61 human tumor cell lines by RT-PCR and its implications for diagnostic and therapeutic procedures. *J. Cancer Res. Clin. Oncol.* 127, 375–386
82 Iurisci, I. *et al.* (2000) Concentrations of galectin-3 in the sera of normal controls and cancer patients. *Clin. Cancer Res.* 6, 1389–1393

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