GALECTINS AS MODULATORS OF TUMOUR PROGRESSION

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Abstract | Galectins are a family of animal lectins with diverse biological activities. They function both extracellularly, by interacting with cell-surface and extracellular matrix glycoproteins and glycolipids, and intracellularly, by interacting with cytoplasmic and nuclear proteins to modulate signalling pathways. Current research indicates that galectins have important roles in cancer; they contribute to neoplastic transformation, tumour cell survival, angiogenesis and tumour metastasis. They can modulate the immune and inflammatory responses and might have a key role helping tumours to escape immune surveillance. How do the different members of the Galectin family contribute to these diverse aspects of tumour biology?

Lectins are carbohydrate-binding proteins that can recognize various carbohydrates attached to proteins and lipids — known as glycoconjugates — on cell surfaces and extracellular matrices. Lectins have many functions, ranging from the mediation of cell adhesion and the promotion of cell–cell interactions to the recognition of pathogens.

Animal lectins are grouped into several families[1–3]. One of these is the galectins (FIG. 1), which are defined by their ability to recognize β-galactose and by their consensus amino-acid sequences[4]. All galectins contain conserved carbohydrate-recognition domains (CRDs) of about 130 amino acids, and these are responsible for carbohydrate binding. To date, fifteen mammalian galectins have been identified, which can be subdivided into those that have one CRD and those that have two CRDs; galectin-3, a one-CRD galectin, is unique in that it contains unusual tandem repeats of short amino-acid stretches fused onto the CRD (reviewed in REFS 5,6) (FIG. 1a). Galectins show a high level of evolutionary conservation, and members of this family are present in organisms from nematodes to mammals[7].

The carbohydrate binding sites of galectins can accommodate adjacent saccharides as well as galactose. Different galectins are specific for different oligosaccharides, as they differ in their ability to accommodate certain saccharides attached to galactose[8,9]. Many galectins are either bivalent or multivalent with regard to their carbohydrate-binding activities: some one-CRD galectins exist as dimers; two-CRD galectins have two carbohydrate-binding sites; and galectin-3 forms oligomers when it binds to multivalent carbohydrates[10] (FIG. 1b). In this way, galectins can form ordered arrays of complexes when they bind to multivalent glycoconjugates, much like the lattices formed by antibodies and multivalent antigens[11].

Galectins do not have a signal sequence, which would be required for protein secretion through the classical secretory pathway. However, some galectins are secreted by the cell, probably through a non-classical secretory pathway, and these galectins can be found in the extracellular space[12,13]. For example, cytosolic galectin-3 can relocalize to the plasma membrane and then become a part of vesicles that extrude from the plasma membrane[13], but the signals that control this are not yet known. Galectins also exist intracellularly and can be detected in subcellular locations such as the nucleus (reviewed in REF. 14).

Some galectins are distributed in a wide variety of tissues, whereas others are more specific. The expression of galectins is modulated during the differentiation of individual cells and during the development of organisms and tissues, and is changed under different physiological or pathological conditions[15]. Interestingly, the expression of galectins is altered in tumour cells compared with their normal counterparts (reviewed in

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doi:10.1038/nrc1527

Summary

- Galectins are a family of animal lectins that have affinity for β-galactosides and that share similar amino-acid sequences.
- Galectins bind to a wide array of glycoproteins and glycolipids both on the cell surface and in extracellular matrices.
- By binding to these glycoconjugates, galectins deliver signals intracellularly as well as mediate cell–cell and cell–extracellular matrix adhesion.
- The most extensively-studied function of galectins is the regulation of apoptosis; some galectins can induce apoptosis when added exogenously to cells, whereas others regulate apoptosis through intracellular mechanisms.
- Galectin-1 and galectin-3 can interact with oncogenic Ras and mediate cell transformation induced by this oncogene.
- Galectins can modulate cell adhesion and cell migration, thereby affecting the process of tumour metastasis.
- Galectin-3 has angiogenic activity.
- Galectins have pro- and anti-inflammatory functions and modulate the immune response. Furthermore, galectin-1 functions as a soluble mediator employed by tumour cells to evade the immune response.

REFS 16–21). Galectins are often overexpressed in cancerous cells and cancer-associated stromal cells, especially in those cell types that do not normally express the specific galectins. However, in some cases, when normal cells do express high levels of selected galectins, these galectins are downregulated when those cells become cancerous. In many situations, this altered galectin expression correlates with the aggressiveness of the tumour and the acquisition of the metastatic phenotype, indicating that galectins might modulate tumour progression and influence disease outcome. It is important to note that a change in the subcellular localization of galectins (for example, from the nucleus to the cytosol) occurs during the transition from normal cells to cancer cells. This change might be related to the cancerous phenotype (reviewed in REF. 17).

There is increasing evidence that galectins have important functions in several aspects of cancer biology, so a review on galectins in cancer is particularly timely. We aim to focus on a number of potential roles for galectins in the regulation of tumour development and growth, including tumour transformation, apoptosis and cell-cycle progression. We also discuss the possible roles of galectins in various steps of tumour metastasis, including their functions in tumour cell adhesion, migration and angiogenesis. We will also discuss the role of galectins in the inflammatory response induced by the tumours and in immune-avoidance by tumour cells.

Intra- and extracellular functions of galectins

Galectins are present both inside and outside cells, and function both intracellularly and extracellularly. Extracellularly, galectins can bind to cell-surface glycoconjugates that contain suitable galactose-containing oligosaccharides. They also bind to some of the glycoproteins in the extracellular matrices, such as laminin, fibronectin, hensin and elastin[22–24]. As galectins can bind either bivalently or multivalently, they can

a

Type	Structure	Galectin
One CRD		1,2,5,7,10,11,13,14,15
		3
Two-CRD		4,6,8,9,12

b

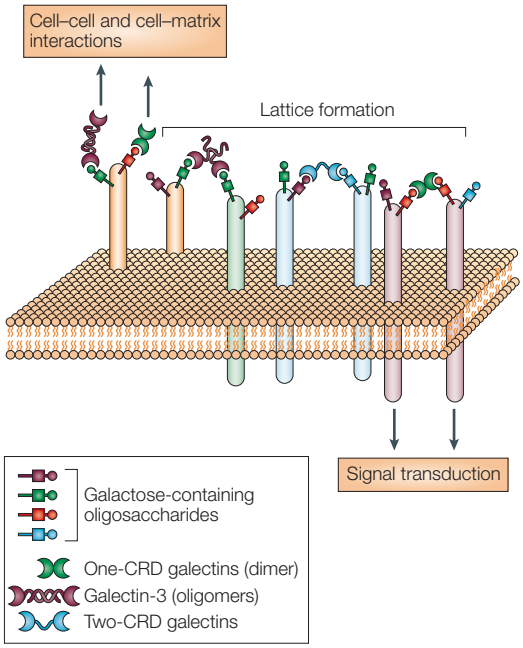

Figure 1 | **The Galectin family. a** | Galectins are a family of animal lectins characterized by conserved carbohydrate-recognition domains (CRDs) consisting of about 130 amino acids that are responsible for carbohydrate binding. So far, 15 mammalian galectins have been identified. They can be subdivided into three groups: those containing one CRD (galectin-1, 2, 5, 7, 10, 11, 13, 14 and 15); those containing two distinct CRDs in tandem, connected by a linker of up to 70 amino acids (galectin-4, 6, 8, 9 and 12); and galectin-3 (Gal-3), which consists of unusual tandem repeats of proline- and glycine-rich short stretches (a total of about 120 amino acids) fused onto the CRD. There are different isoforms of two-CRD type galectins, and these vary with respect to the length of the linker. **b** | Many galectins are either bivalent or multivalent with respect to their carbohydrate-binding activities: some one-CRD galectins exist as dimers; two-CRD galectins have two carbohydrate-binding sites; and galectin-3 forms oligomers when it binds to multivalent carbohydrates. Galectins can interact with cell-surface glycoconjugates, some of which are transmembrane proteins. Galectins can crosslink some of these glycoconjugates and trigger a cascade of transmembrane signalling events. Although binding to only two glycocoproteins is shown here, galectins can potentially cause the clustering of multiple multivalent glycoconjugates, resulting in a lattice formation. They can also bridge two cells of the same or different types, and bridge cells to extracellular matrix proteins. For simplicity, saccharides recognized by galectins are shown here as disaccharides, but they are likely to be oligosaccharides. In addition, the different colours of the saccharides shown here reflect the fact that different galectins bind to different sets of oligosaccharides.

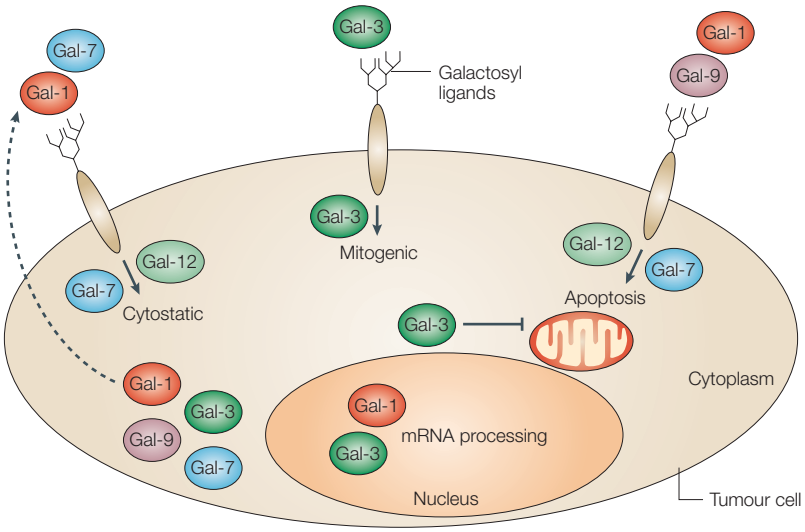

Figure 2 | **Intracellular and extracellular functions of galectins.** Galectins (shown here as Gal-1–Gal-12) can be intracellularly located or secreted into the extracellular space. Extracellularly, they can crosslink cell-surface glycoconjugates that are decorated by suitable galactose-containing oligosaccharides and can deliver signals inside the cell. Through this mechanism, they modulate mitosis, apoptosis and cell-cycle progression. Intracellularly, galectins shuttle between the nucleus and cytoplasm and are engaged in fundamental processes such as pre-mRNA splicing. They can also regulate cell growth, cell-cycle progression and apoptosis by interacting with the relevant intracellular signal-regulation pathways. Although the galactosyl ligands recognized by galectins have been drawn to be the same in this figure, galectins have high specificity **[AU: Okay?]** for oligosaccharides, and each can bind to a different set of glycoconjugates. Also, although we have not explicitly shown them here, galectins can bind to both glycolipids and glycoproteins.

crosslink cell-surface glycoconjugates, which, like many other receptor-ligand systems, can trigger a cascade of transmembrane signalling events (FIG. 1). Through this mechanism, galectins modulate processes that include mitosis, apoptosis and cell-cycle progression (FIG. 2). Galectins' bivalent and multivalent properties also enable them to bridge two cells of the same or different type; this allows homo- or heterotypic aggregation, as well as the bridging of cells to extracellular matrix proteins (FIG. 1).

Intracellularly, galectins shuttle between the nucleus and cytoplasm[25] and are engaged in processes that are essential for basic cellular functions, such as pre-mRNA splicing[26–28] and the regulation of cell growth, apoptosis and cell-cycle progression (FIG. 2). The exact mechanisms by which galectins regulate these processes are not known. However, galectins do interact with a number of intracellular proteins that are involved in the regulation of these processes[14,28] (see below). Importantly, in most cases, protein–protein interactions, rather than lectin–carbohydrate interactions are involved. The galectin-interacting proteins that have been identified so far are not structurally related to each other and do not seem to share common domains or motifs. The sites in galectins that are involved in these interactions have not yet been established.

Galectins in tumour transformation and survival

Cancer development is initiated when normal cells undergo neoplastic transformation, the cumulative result of dysregulation in cell growth-regulatory mechanisms that include defective apoptosis and cell-cycle alterations. A number of galectins are associated with these processes (FIG. 3).

Involvement in tumour transformation. There is direct evidence that galectin-1 and galectin-3 expression is necessary for the initiation of the transformed phenotype of tumours. Inhibition of galectin-1 expression suppresses the transformed phenotype of human glioma cells (as determined by the cell morphology)[29]. In addition, following the inhibition of galectin-3 expression, breast carcinoma cells and thyroid papillary carcinoma cells lose their characteristic transformed phenotypes in cell culture[30,31]. Conversely, the introduction of galectin-3 cDNA into a normal thyroid follicular cell line induces a transformed phenotype[32].

The mechanisms by which galectins are involved in cell transformation are not yet fully understood, but both galectin-1 and galectin-3 can interact with oncogenic Ras[33,34] (FIG. 3). Human tumours frequently express Ras proteins with point mutations that make them constitutively active, and the most commonly affected Ras proteins are HRAS, KRAS (also known as KRAS2), and NRAS. Oncogenic Ras proteins contribute to various aspects of the malignant phenotype and their activities require that they are anchored to the plasma membrane. Kloog and colleagues demonstrated that this membrane anchorage requires galectin-1 to function as an interacting partner of oncogenic HRAS[33] (FIG. 3). Overexpression of galectin-1 in tumour cells results in an increase in both the membrane association of oncogenic Ras and cell transformation, the latter being determined by focus formation assays[33]. The researchers also showed that galectin-1 expression results in the sustained activation of RAF1 and extracellular signal-regulated kinase (ERK)[35]. They proposed that, in turn, these downstream signalling molecules activate transcription factors and promote transformation by inducing aberrant gene expression (FIG. 3). Inhibition of galectin-1 expression using an antisense RNA abolished the membrane anchorage of oncogenic HRAS and inhibited the transformation induced by this protein. Kloog and colleagues subsequently found that galectin-3 also binds to oncogenic Ras proteins, but preferentially to KRAS. As a result, galectin-3 promotes the activation of RAF1 and phosphatidylinositol 3-kinase (PI3K)[34], and contributes to the selective activation of signalling cascades and the regulation of gene expression at the transcriptional level. Therefore, the galectin family might have an important role in the membrane anchorage of RAS and in RAS-mediated cell transformation.

Regulation of apoptosis. The most extensively-studied function of galectins that is relevant to tumour progression is the regulation of apoptosis (FIG. 3), and this has been demonstrated mainly by using two different approaches. In the first approach, recombinant galectin proteins that were exogenously added to cells — including tumour cells — were shown to induce apoptosis, probably through the binding of galectins to cell-surface glycoconjugates (discussed in a later section). The second

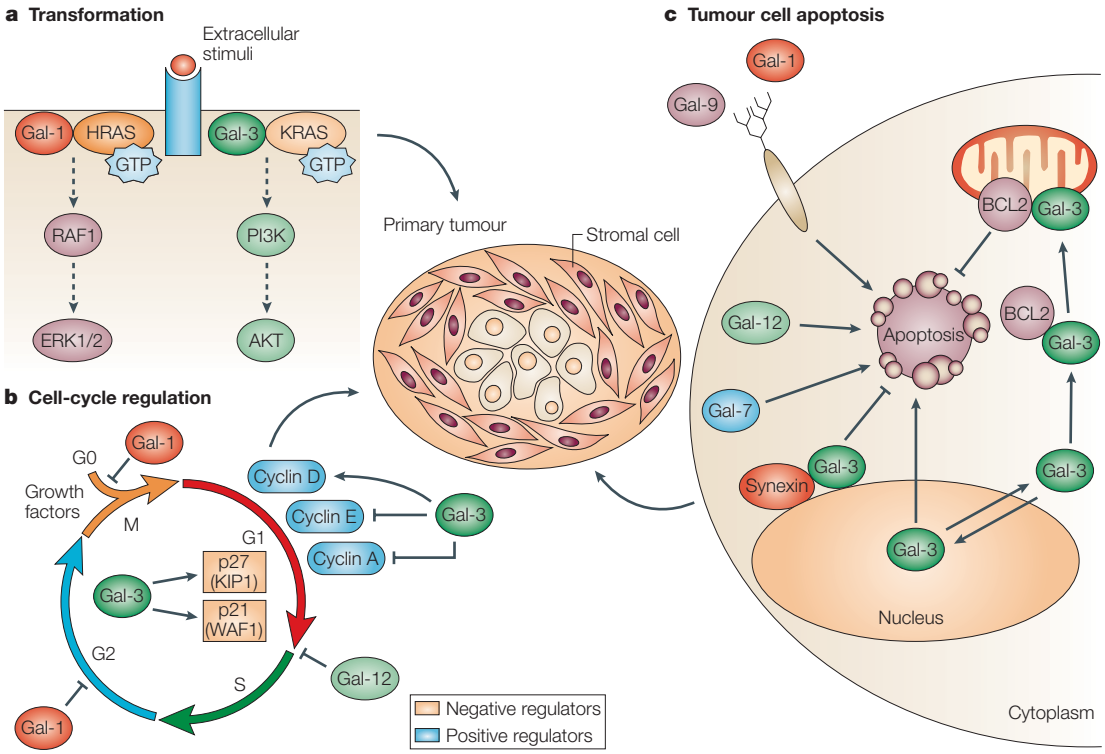

Figure 3 | **Roles of galectins in tumorigenesis.** Galectins might have important roles during different steps of tumorigenic processes, including tumour cell transformation, cell-cycle regulation and apoptosis. **a** | Galectin-1 (Gal-1) and Gal-3 can mediate neoplastic transformation by interacting with oncogenes, such as oncogenic Ras (HRAS and KRAS shown here), and promote Ras-mediated signal transduction (shown here to involve RAF1, extracellular signal-regulated kinase (ERK) 1/2, phosphatidylinositol-3-kinase (PI3K) and the serine/threonine kinase AKT). **b** | Galectins can also control tumour progression by modulating cell-cycle progression. In particular, Gal-3 regulates the levels of known cell-cycle regulators (including cyclin A, E and D), as well as the cell-cycle inhibitors p21 (WAF 1) and p27 (KIP1), resulting in cell cycle arrest. Gal-1 and Gal-12 induce arrest at various stages of the cell cycle, although the molecular mechanisms of this have not been elucidated. **c** | Galectins regulate apoptosis. Gal-1 and Gal–9 can induce tumour cell apoptosis when added exogenously to the cell, whereas Gal-7 and Gal-12 promote apoptosis through intracellular mechanisms. Gal-3 has anti-apoptotic functions and it translocates to the perinuclear membrane and to the mitochondria in cells exposed to apoptotic stimuli. The translocation is dependent on synexin, a phospholipid- and Ca^{2+}-binding protein, which has been identified as one of the Gal-3-interacting proteins. Gal-3 might also function by interacting with intracellular apoptosis regulators such as B-cell lymphoma 2 (BCL2), or might facilitate the localization of BCL2 to the mitochondria, although definitive evidence for such a function is lacking. The effect of Gal-3 in the regulation of apoptosis depends on its subcellular localization: cytoplasmic Gal-3 is anti-apoptotic, whereas nuclear Gal-3 is pro-apoptotic.

approach was the study of tumour cells transfected with a cDNA encoding an individual galectin. This approach, used in both our laboratory and other research groups, was most successful for galectin-3, clearly demonstrating its anti-apoptotic activity in a range of tumour cell types exposed to diverse apoptotic stimuli (reviewed in REF. 14). Galectin-3 anti-apoptotic activity was also confirmed by the demonstration that galectin-3-positive cells transfected with a gene encoding an amino-terminal truncated galectin-3 (which, when expressed, functions in a dominant-negative fashion) had increased sensitivity to apoptotic stimuli[36]. Importantly, the anti-apoptotic activity of galectin-3 can also regulate the susceptibility of tumour cells to apoptosis induced by chemotherapeutic agents[37,38].

The anti-apoptotic activity of galectin-3 is not completely understood, but the protein has been shown to translocate either from the cytosol or from the nucleus to the mitochondria following exposure to apoptotic stimuli[39] and to block changes of the mitochondrial membrane potential, thereby preventing apoptosis[40]. Therefore, galectin-3 might exert its anti-apoptotic activity by interacting with other apoptosis regulators that function in the mitochondria (see below).

Galectin-3 is phosphorylated by casein kinase I *in vitro* at Ser6 (REF. 41) and it exists in this phosphorylated form inside the cell[42]. Raz and colleagues demonstrated that when this serine residue is mutated to alanine or glutamic acid, galectin-3 cannot be phosphorylated and its anti-apoptotic activity is decreased[43], indicating that phosphorylation at this position is crucial for the protein's anti-apoptotic activity. Moreover, phosphorylation is necessary for the export of galectin-3 from the nucleus when the cells are exposed to apoptotic stimuli. In turn, phosphorylated galectin-3 upregulates the mitogen activated protein kinase (MAPK) pathway, which is involved in regulation of apoptosis[37].

Galectin-3 has significant sequence similarity to B-cell lymphoma 2 (BCL2), which is a well-characterized suppressor of apoptosis[44]. In particular, they both

contain an Asp-Trp-Gly-Arg (NWGR) motif in the carboxyl-terminal part of the molecule, a sequence that is highly conserved among members of the Bcl2 family and is essential for their function during apoptosis-regulation. This motif is present in galectin-3 proteins from many different animal species and is required for carbohydrate-binding activity. Substitution of glycine to alanine in this motif abrogates the anti-apoptotic activity of galectin-3 (REF. 45), highlighting the importance of this motif in this activity. However, it is not clear whether the motif in galectin-3 functions in the same manner as it does in BCL2.

BCL2 can bind to galectin-3 that is immobilized on Sepharose beads *in vitro*, and this interaction is inhibited by lactose. However, a direct interaction between the two proteins and their intracellular association have not been established. If there is such an interaction, it is possible that galectin-3 exerts its anti-apoptotic effects by binding to BCL2 or by mediating the transport of BCL2 to the mitochondria (FIG. 3).

Other intracellular proteins could also be involved in the anti-apoptotic activity of galectin-3. For example, synexin (also called annexin VII), a Ca^{2+}- and phospholipid-binding protein, is a galectin-3-interacting protein, and is necessary for the translocation of galectin-3 to the perinuclear membranes in cells treated with apoptotic stimuli[39] (FIG. 3). Current evidence indicates that the mechanisms through which galectin-3 inhibits apoptosis are complex and are dependent on galectin-3 localization. Specifically, recent experimental evidence indicates that galectin-3 localized in the cytosol protects the cell from apoptosis, but that galectin-3 localized in the nucleus has the opposite effect[46].

Other galectins can also regulate apoptosis, but much less is known about the possible mechanisms by which they do this (reviewed in REF. 47). We and other research groups have shown that transfected tumour cells that overexpress galectin-7 are more likely than control cells to undergo apoptosis induced by a number of different apoptotic stimuli that trigger different signalling pathways[48,49]. Galectin-12 promotes apoptosis when it is overexpressed in a fibroblast cell line[50]. Both galectins are believed to regulate apoptosis by functioning intracellularly; however, definitive evidence for this is lacking.

In summary, some galectins are pro-apoptotic, whereas others are anti-apoptotic. Some galectins induce apoptosis by binding to cell-surface glycoproteins, and others regulate apoptosis through interacting with relevant intracellular proteins. Much remains to be learned about how various galectins induce or inhibit apoptosis. One concern about the use of the galectin gene transfection approach is that the overexpression of a protein might induce some alterations in cellular properties and that the observed phenotype might not be directly relevant to the function of this protein. In this regard, it is reassuring that we have obtained additional evidence for the anti-apoptotic function of galectin-3 by studying MACROPHAGES from galectin-3-deficient mice[51]. Additional studies using small interfering RNA (siRNA) or cancer cells grown in galectin-specific knock-out mice will be useful for definitively establishing the apoptosis-regulating activity of various galectins. Finally, tumour cells can undergo non-apoptotic death, such as necrosis, senescence and autophagy[52]; a crucial question for the future is whether galectins can regulate these processes.

Other effects of galectins on tumorigenesis. Galectins regulate cell growth, and in some cases this has been shown to be independent of the role of galectins during apoptosis. For example, galectin-1 can function as an autocrine cell growth suppressor[53], and both galectin-1 and galectin-7 inhibit the growth of neuroblastoma cells when added exogenously[54,55]. Many groups have studied the role of galectin-3 in the regulation of tumour growth, either by transfecting cDNA into cell lines or by using an anti-sense approach to inhibit gene expression (reviewed in REF. 47). We found that human T lymphoma Jurkat cells transfected with galectin-3 grow faster than controls *in vitro*. Raz and colleagues showed that inhibition of galectin-3 expression in breast carcinoma cells and thyroid papillary carcinoma cells results in slower growth *in vivo*[30,31]. van den Brule, Castronovo and colleagues showed that the human breast cancer MDA-MB-435 cells transfected with antisense galectin-3 cDNA have significantly decreased cell proliferation, as measured by thymidine incorporation, compared with control transfectants[56]. These results indicate that galectin-3 is a positive growth regulator. However, the prostate cancer cell line LNCaP transfected with galectin-3 grows slower than controls both *in vitro* and *in vivo*[57].

These variable effects of galectin-3 on cell growth were explained in a recent study by van den Brule, Castronovo and colleagues. They found that LNCaP cells that express transgenic galectin-3 in the cytosol exhibit increased anchorage-independent growth *in vitro* and increased tumour growth *in vivo*, whereas those that express the protein in the nucleus grow slower[46]. The results indicate that the effect of endogenous galectin-3 on tumour growth depends on the subcellular localization of the protein. The mechanisms by which galectin-3 regulates cell proliferation are not well understood, but recent data indicate that galectin-3 upregulates and interacts with the homeodomain-containing thyroid-specific transcription factor TTF1 (also known as TITF1), which is involved in thyroid cell proliferation[58]. Therefore, it is possible that galectin-3 controls cell proliferation by interacting with TTF1 and other transcription factors.

Similar gene transfection approaches have been used to show that other galectins also regulate cell growth. For example, the inhibition of galectin-1 expression in human glioma cells suppresses the anchorage-independent growth of the cells[29]. We found that a colon carcinoma cell line that expresses transgenic galectin-7 grows slower than controls[59]. This occurs in the absence of detectable apoptosis, indicating that this galectin is a cell

MACROPHAGES
Cells of the mononuclear-phagocyte system that can phagocytose foreign particulate materials. Macrophages are present in many tissues and are important for the innate and immune reactions. They can also function as antigen-presenting cells and as effector cells in humoral and cell-mediated adaptive immunity. They have a vital role in host defense.

SCID MICE
Mice that are homozygous for the severe combined immunodeficiency (SCID) mutation have compromised B- and T-cell immunity. This lack of immunity means that they can support human tumour xenografts for preclinical studies.

growth suppressor. We also found that the growth of tumours derived from galectin-7-expressing cells in SCID MICE is dramatically reduced compared with control cells[59]. These results could be due to the combination of the pro-apoptotic and growth-suppressing effects of galectin-7.

Finally, galectins might regulate tumorigenesis by regulating the cell cycle (FIG. 3). Raz and colleagues provided experimental evidence from studying breast cancer cells *in vitro* that galectin-3 affects known cell-cycle regulators. This includes the downregulation of cyclin E and cyclin A (cyclins involved in progression from G1 to S phase), the upregulation of the cell-cycle inhibitors p21 (WAF1) and p27 (KIP1), and the induction of cyclin D1 (a cyclin expressed in early G1 phase)[60] (FIG. 3). Subsequent studies indicate that galectin-3 can activate the cyclin D1 promoter[61]. In a more recent study, this group demonstrated that galectin-3 binds to β-catenin, an intracellular protein implicated in the regulation of cell cycle progression, and they proposed that galectin-3 activates cyclin D1 by binding to β-catenin[62]. There is also evidence that implicates galectin-12 in the regulation of the cell cycle[63]. However, whether galectins modulate tumour development through the regulation of cell-cycle progression remains to be determined.

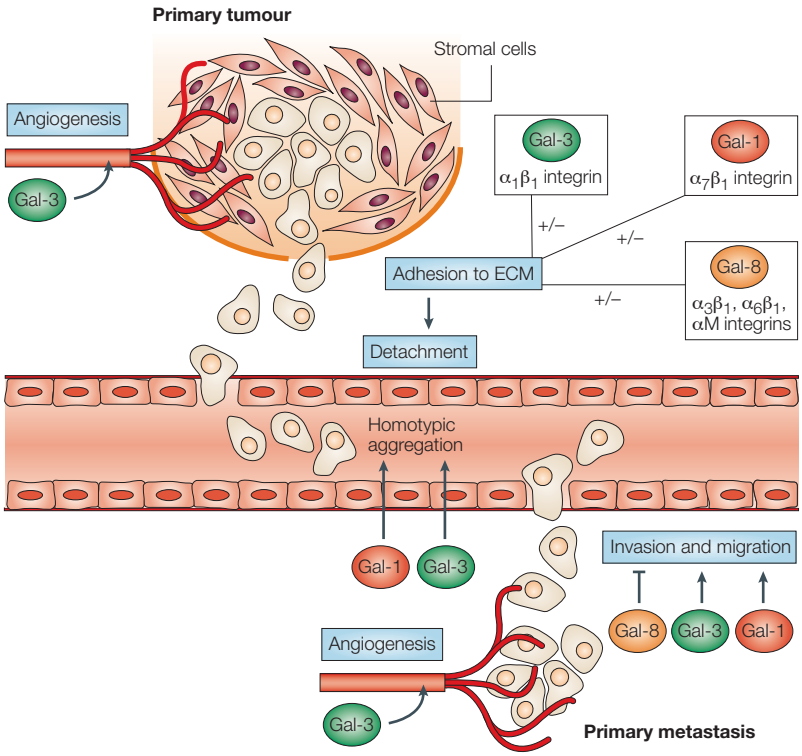

Figure 4 | **Galectins and tumour metastasis.** The progression from primary to metastatic tumours is a multigenic and multistep process that involves cell–cell and cell–extracellular matrix (ECM) adhesion, cell invasion and/or migration and angiogenesis. Different galectins seem to have key roles at different steps of the processes. Some members function together with integrins to mediate tumour cell adhesion, including adhesion to ECM proteins and homotypic cell adhesion, but can also inhibit adhesion, which could result in tumour cell detachment. The overall effect can be either the promotion or the inhibition of metastasis. Galectin-1 (Gal-1), Gal-3, and Gal-8 can influence tumour 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 remodelling cytoskeletal elements associated with cell spreading — microfilaments — through as yet unidentified mechanisms. Gal-3 can promote angiogenesis by promoting endothelial cell migration. A number of galectins bind to different integrins, which have an important role in tumour metastasis by regulating cell adhesion and migration (as well as cell survival and angiogenesis). Whether the overall consequence of these effects is the promotion or inhibition of metastasis remains to be elucidated.

Galectins in tumour metastasis

Tumour metastasis involves the invasion of the tumour into surrounding tissues, dissemination through blood or lymph vessels and growth at distant sites. Factors involved in tumour metastasis include changes in cell adhesion, increased migration or motility and invasiveness, angiogenesis and evasion of the immune response. Various different galectins have been shown to contribute to all of these processes, as discussed in this and subsequent sections. These recent discoveries indicate that the Galectin family as a whole might be important to tumour metastasis (FIG. 4).

Effects on cell adhesion during metastasis. Metastasis involves many changes in cell–cell and cell–extracellular matrix interactions, and these include the detachment of cells from the primary tumour and their attachment to endothelial cells or basement membrane proteins at distal sites. *In vitro* studies have demonstrated that various different galectins might be involved in each of these processes (FIG. 4).

It has been extensively documented that loss of intercellular adhesion is correlated with tumour invasion and metastasis[64]. This loss of adhesion occurs during the initiation of metastasis, allowing tumour cells to leave the initial tumour site. As they can bind to cell-surface glycoproteins, galectins that are released by tumour cells might perturb the adhesion between adjacent cancer cells or between cancer cells and extracellular matrices. Galectins might do this either by directly binding to molecules involved in cell adhesion or by steric hindrance of the normal interactions between cell-adhesion molecules that enable them to maintain cell–cell or cell–matrix interactions. In fact, exogenously added recombinant galectin-1 and galectin-3 inhibit the adhesion of tumour cells to extracellular matrix proteins (reviewed in REFS 22,65,66). Similarly, soluble galectin-8 inhibits the adhesion of a number of different cell lines to culture plates[67]. If this mechanism operates in tumours, it is feasible that galectins will augment the detachment of tumour cells and promote metastasis.

Alternatively, because of their bivalent or multivalent properties, galectins might be able to form a bridge between cells or between cells and the extracellular matrix, thereby promoting cell adhesion, and this has been demonstrated in certain situations. By this mechanism, galectins would suppress the detachment of cells from the primary sites but would promote tumour cell–cell (homotypic) adhesion as well as attachment of tumour cells to the endothelial cells (heterotypic adhesion) at distal sites during the process of metastasis. For example, galectin-1 promotes the adhesion of ovarian and prostate cancer cell lines to the extracellular matrix[68,69]. Furthermore, immunofluorescence staining of cancer cell aggregates showed that galectin-3 is clustered at the sites of

cell–cell contact[70], indicating that the protein is involved in homotypic tumour cell adhesion. Whether, in these cases, galectins increase or decrease the metastatic properties of these cells remains to be studied. In addition, highly metastatic human breast carcinoma cells express higher levels of galectin-3 and have significantly increased adhesion to monolayers of endothelial cells *in vitro* compared with their non-metastatic counterparts[71]. The involvement of galectin-3 in this adhesive process is indicated by the inhibition of adhesion by a glyco-amino acid that binds to and inhibits galectin-3, as well as the detection of galectin-3 at the adhesion contact sites[71]. The overall effects of galectins on cell adhesion during metastasis probably depend on which particular galectins and which subsets of the galectin-interacting glycoconjugates are expressed in tumours, as well as whether these glycoconjugates are involved in cell adhesion[22]. Whether the results obtained by using exogenously added galectins *in vitro* are relevant *in vivo* also remains to be determined.

Interestingly, galectins recognize, in a carbohydrate-dependent manner, one of the most extensively studied families of cell adhesion molecules, the integrins. For example, galectin-1 binds to α7β1 (REF. 72), galectin-3 binds to α1β1 (REF. 73), and galectin-8 binds to α3β1 and α6β1 (REF. 67) as well as αM[74] (FIG. 4). Therefore, the effects of galectins on cell adhesion described above could be mediated by galectins binding to these integrins. In addition, galectin-3 can upregulate integrin expression[75]. Integrins play an important part in tumour metastasis through their adhesive interactions with extracellular matrices (reviewed in REF. 64). Galectins might modulate tumour metastasis by binding to integrins or by regulating their expression.

Regulation of tumour invasiveness. Galectins have been shown to affect the motility of tumour cells and influence their invasiveness in *in vitro* tumour invasion assays (FIG. 4). This was demonstrated by adding galectins exogenously to cells and by overexpressing them in tumour cells. The addition of galectin-3 to breast carcinoma cells markedly enhanced the migration of the cells through a Matrigel barrier[76], probably owing to the binding of galectin-3 to cell-surface receptors involved in cell migration. By contrast, another study showed that exogenously added galectin-3 reduced the migration of human colon cancer cell lines[77]. The reasons for these opposing results are not clear, but they could be due to the difference in the cell-surface receptors that are recognized by galectin-3, and the effects of these cell surface receptors on cell migration. A lung cancer cell line overexpressing galectin-3 has enhanced cell motility and invasiveness *in vitro*[78], indicating that endogenous galectin-3 can regulate cell migration. Furthermore, the overexpression of galectin-3 in human breast carcinoma cells results in the remodelling of those cytoskeletal elements associated with cell spreading: that is, microfilaments[75]. Whether the results are due to galectin-3 functioning intracellularly or extracellularly is not known.

The roles for other galectins in cell motility and tumour invasion have also been documented. The level of galectin-1 expression is positively correlated with the migratory phenotype and biological aggressiveness of human astrocyte tumours[79]. In addition, exogenously added galectin-1 causes increased motility of astrocyte tumour cells *in vitro*[79]. These results indicate that galectin-1 might positively regulate the migration and invasiveness of tumours. Conversely, exogenously added galectin-8 reduces the migration of some colon cancer cell lines *in vitro*[80], indicating that it is a negative regulator of tumour cell migration.

As mentioned above, galectins bind to integrins and galectin-3 upregulates integrin expression. As integrins have an important role in controlling cell migration and therefore tumour invasion[64], it is possible that galectins regulate tumour cell motility and invasion by involving the activation or expression of integrins. In fact, galectin-8 ligates integrins and triggers integrin-mediated signalling cascades, resulting in cytoskeletal changes and cell spreading[67]. Therefore, existing information indicates that galectins can contribute to cell motility and invasiveness by several mechanisms. Extracellularly, they can engage integrins or other cell-surface proteins involved in cell migration. Intracellularly, they might affect the intrinsic motility of cells through as yet unidentified mechanisms.

Regulation of tumour angiogenesis. Angiogenesis is required for invasive tumour growth and metastasis and constitutes an important process in cancer progression[81]. Galectin-3 has angiogenic activity *in vitro*, and this might be related to its ability to induce the migration of endothelial cells[82]. When transplanted into immunocompromised mice, human breast tumour cells that overexpress galectin-3 show an increase in the density of capillaries that surround the tumour compared with controls[82]. This supports the hypothesis that galectin-3 secreted by tumour cells induces angiogenesis (FIG. 4), and similar results have been documented in LNCaP cells that express transgenic galectin-3 (REF. 46). Whether other galectins have a role in angiogenesis remains to be determined.

Finally, extracellular galectins might influence tumour progression by modulating the endocytosis of key receptors involved in various steps of tumour progression. For example, galectin-3 induces the endocytosis of β1 integrins in breast carcinoma cells[83], but impedes the endocytosis of epidermal growth factor and transforming growth factor-β receptors by binding to these receptors[84]. Furthermore, the effects of the galectins described above might be affected by other factors. For example, there is evidence that galectin-3 is cleaved by matrix metalloproteases, and therefore its biological activity in the various steps in the metastatic process might be controlled by the enzymes that are present in the tumour microenvironment[85].

In vivo *effects of galectins on metastasis.* The overall effects of galectins *in vivo* could be the combination of some or all of the effects described above. Studies using

Box 1 | **Mechanism of tumour-immune escape**

Despite the existence of tumour-specific immune cells, tumours have devised multiple strategies for evading the immune system. These include the alteration of different components of the antigen processing and presentation machinery, and the production of immunosuppressive cytokines and other soluble factors, including transforming growth factor-β (TGFβ), interleukin 10 (IL10) and vascular endothelial growth factor (VEGF).

The tumour microenvironment also promotes the accumulation of regulatory T cells that inhibit the functions of other T cells[93]. The hypothesis of 'tumour counterattack' proposes that cancer cells can deliver death signals to Fas (CD95)-sensitive effector immune cells by expressing Fas (CD95) ligand, causing tumours to become immunologically privileged sites[142].

Although this hypothesis has not been universally accepted, recent studies highlight the contribution of novel tumour-associated molecules to tumour-immune evasion, including B7-H1 and the enzyme indoleamine 2,3 dioxigenase (IDO). B7-H1 is a member of the B7 family of co-stimulatory molecules that can induce T-cell apoptosis[143], and IDO is an enzyme that catalyses the initial step during the catabolism of tryptophan, promoting the arrest of T-cell proliferation at the tumour site by tryptophan deprivation[144]. Furthermore, accumulating evidence indicates the importance of negative regulatory pathways — including cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the Janus kinase 2 (JAK2)–signal transducer and activator of transcription 3 (STAT3) pathway — that, by counteracting effector mechanisms, greatly influence the magnitude of antitumour responses[145]. It has recently been reported that the activation of the oncogenic STAT3 signalling pathway suppresses the production and sensing of inflammatory signals by multiple components of the immune system[145]. In this context, tumour-secreted galectin-1 contributes to the immune escape of tumours by modulating the survival of effector T cells and by skewing the balance of the immune response towards an anti-inflammatory cytokine profile. It has been suggested that blocking these different inhibitory signals might be effective in combination with other immunotherapy strategies, such as cytokine gene transfer or DENDRITIC CELL vaccination, to overcome immunological tolerance and promote tumour regression[93,94].

animal models have provided evidence for the role of galectins in tumour metastasis *in vivo*[86,87]. In addition, liver metastases of human adenocarcinoma xenotransplants in SCID mice are inhibited by an anti-galectin-3 antibody[88]. Finally, during the process of metastases, tumour cells can encounter conditions that affect their survival; therefore galectin-3 can also contribute to the survival of metastasizing tumour cells by preventing apoptosis. Indeed, in a metastatic model, breast carcinoma cells that overexpress transgenic galectin-3 are more resistant to apoptosis induced by reactive nitrogen and oxygen species (which are believed to be generated when tumour cells lodge in microcapillaries causing local ischemia and reperfusion injury) than control breast carcinoma cells, and therefore also have a higher metastatic potential[89].

Galectins and the tumour immune response

Tumour cells express proteins that appear immunologically foreign to the host and therefore might be recognized by specific immune effectors. In addition, proteins that are expressed transiently or at very low levels by normal cells can be constitutively overexpressed by cancer cells, making these proteins more visible to the immune effectors. The immune effectors include $CD4^+$ and $CD8^+$ cells, which, in combination, are believed to be the most effective way of eliminating a tumour mass. In addition, $CD4^+$ and $CD8^+$ cells can orchestrate the recruitment of other immune and inflammatory cells. Tumour cells also secrete various cytokines and chemokines, which can influence the immune and inflammatory responses surrounding the tumours. Whereas some inflammatory cytokines and chemokines create an appropriate setting to suppress tumour growth and kill cancer cells, others have a positive impact on tumour progression and survival[90–92]. Furthermore, tumour cells can release mediators believed to contribute to tumour cell evasion of the immune response[93–95] (BOX 1).

Galectins are expressed by many different immune and inflammatory cells and regulate the functions of these cells (reviewed in REF. 96) (FIG. 5). Therefore, it is conceivable that they can affect the immune and inflammatory responses developed by the host against tumours. In addition, galectins are released by tumours and, like cytokines and chemokines, can modulate a variety of inflammatory responses (reviewed in REFS 96–100) (FIG. 5). Some galectins are amplifiers of the inflammatory response, whereas others activate homeostatic signals to shut off immune effector functions[101]. Importantly, recent data indicate that some galectins released by the tumour might help the tumour to evade the immune surveillance.

Galectin-1. The most extensively studied galectin in the context of regulation of the immune response is galectin-1. Galectin-1 inhibits full T-cell activation[102], induces the growth arrest and apoptosis of activated T cells[103–107], and suppresses the secretion of pro-inflammatory cytokines[108]. All of these activities have been demonstrated by adding exogenous galectin-1 to T cells *in vitro*, but often the activities require a relatively high concentration of galectin-1. However, galectin-1 presented by the extracellular matrix induces apoptosis significantly more effectively in T-cell lines than simple exogenous application[107]. *In vivo* evidence for the role of galectin-1 in the inflammatory response has also been accumulating. Administration of galectin-1 suppresses T-cell dependent responses in experimental models of autoimmunity and GRAFT-VERSUS-HOST DISEASE[109–111]. In the autoimmunity models, galectin-1 increases T-cell susceptibility to activation-induced apoptosis, skewing the balance of the immune response towards an anti-inflammatory cytokine profile.

As galectins are bivalent or multivalent and can bind to cell-surface glycoconjugates, their effects on immune and inflammatory cells are likely to be due to the binding and crosslinking of cell-surface glycoproteins on these cells[112]. Galectin-1 recognizes a number of cell-surface glycoproteins in T-cell lines — including the signalling proteins CD2, CD3, CD7, CD43 and CD45 — in a carbohydrate-dependent manner, and can cause a redistribution of some of these proteins into segregated microdomains within the plasma membrane[113]. The signal transduction events that lead to apoptosis induced by galectin-1 involve several intracellular mediators of apoptosis, including the induction of specific transcription factors, the modulation of BCL2 protein production, and the activation of caspases[114–116]. However, a recent study shows that apoptosis induced by galectin-1 in a T-cell line is not

DENDRITIC CELL
Specialized antigen-presenting cell whose immunogenicity leads to the induction of antigen-specific immune responses. Dendritic cells have been used in numerous clinical trials to induce anti-tumour immune responses in cancer patients.

GRAFT-VERSUS-HOST DISEASE
In organ transplantation, mature T lymphocytes from the donor can attack various tissues in the recipient, causing a graft-versus-host (GVH) reaction and a disease state termed graft-versus-host disease.

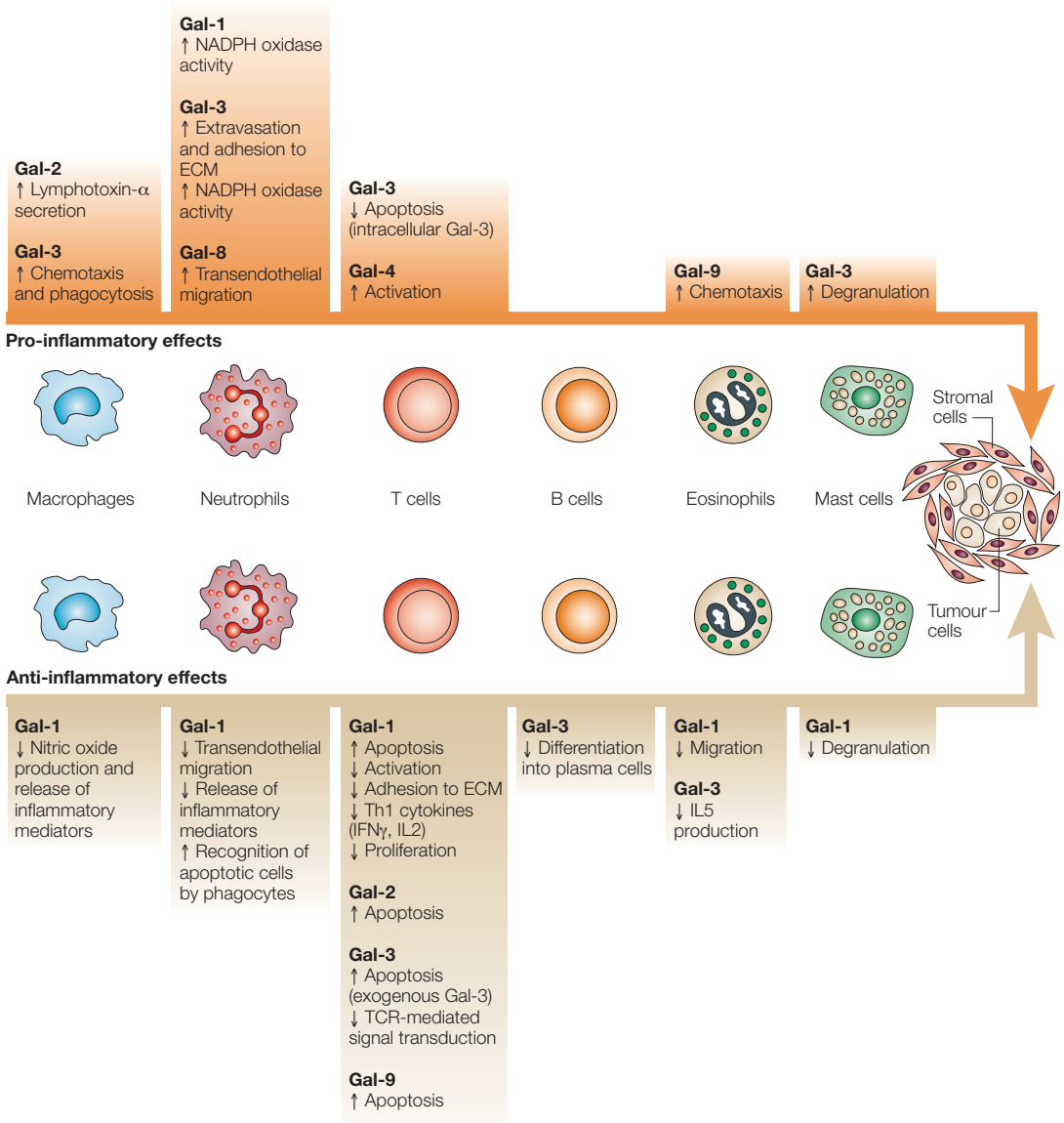

Figure 5 | **Galectins and tumour-associated immune and inflammatory responses.** Galectins (shown here as Gal-1–Gal-9) are expressed by a number of different immune cells and inflammatory cells and regulate the functions of these cells, thereby affecting the immune and inflammatory responses developed by the host against tumours. In addition, galectins released by the tumours can modulate various inflammatory responses. As shown in this diagram, galectins can behave as pro-inflammatory or anti-inflammatory mediators by modulating the physiology and responses of immune cells, including macrophages, T and B cells, neutrophils, EOSINOPHILS and MAST CELLS. There is increasing evidence that some tumour-associated inflammatory responses have a positive impact on tumour progression and survival, whereas others can inhibit tumour growth and kill cancer cells. By positively or negatively (indicated by upwards and downwards arrows) affecting the inflammatory response surrounding the tumours, galectins indirectly influence tumour progression and metastasis. ECM, extracellular matrix; IL2, interleukin 2; IL5, interleukin 5; IFNγ, interferon γ; NADPH, nicotinamide adenine dinucleotide phosphate, reduced form; TCR, T-cell receptor.

NEUTROPHILS
The major class of white blood cells in human peripheral blood (>70%). Neutrophils are phagocytes and have an important role in engulfing and killing extracellular pathogens. They can migrate into tissues under the influence of chemotactic stimuli, where they phagocytose materials.

EOSINOPHILS
White blood cells thought to be important chiefly in defense against parasite infections and in allergic inflammation. However, they can be activated by lymphocytes of the adaptive immune response and have a role in tumour immunity.

MAST CELLS
Bone marrow-derived leukocytes that reside in almost all tissues. They are the key cell type responsible for allergic reactions, but also have an important role in adaptive and innate immunity.

dependent on the activation of caspase-3 or on cytochrome *c* release — two hallmarks of apoptosis — implying that galectin-1 might not trigger a full apoptotic pathway[116]. Furthermore, recent evidence also indicates that galectin-1 can induce the exposure of phosphatidylserine (an early apoptotic marker involved in the phagocytosis of apoptotic cells) on the plasma membrane of the human T leukaemia MOLT-4 cells (as well as on a human promyelocytic cell line and activated NEUTROPHILS), but that this does not result in apoptosis[117]. Therefore, galectin-1 might activate different death pathways or different apoptosis end points in different cell types.

The correlation between galectin-1 expression and the aggressiveness of different tumour types[16,17], in conjunction with its immunoregulatory effects, indicates that tumour cells might impair T-cell effector functions by secreting galectin-1, thereby tilting the balance towards an immunosuppressive environment at the tumour site (FIG. 6). Indeed, by a combination of

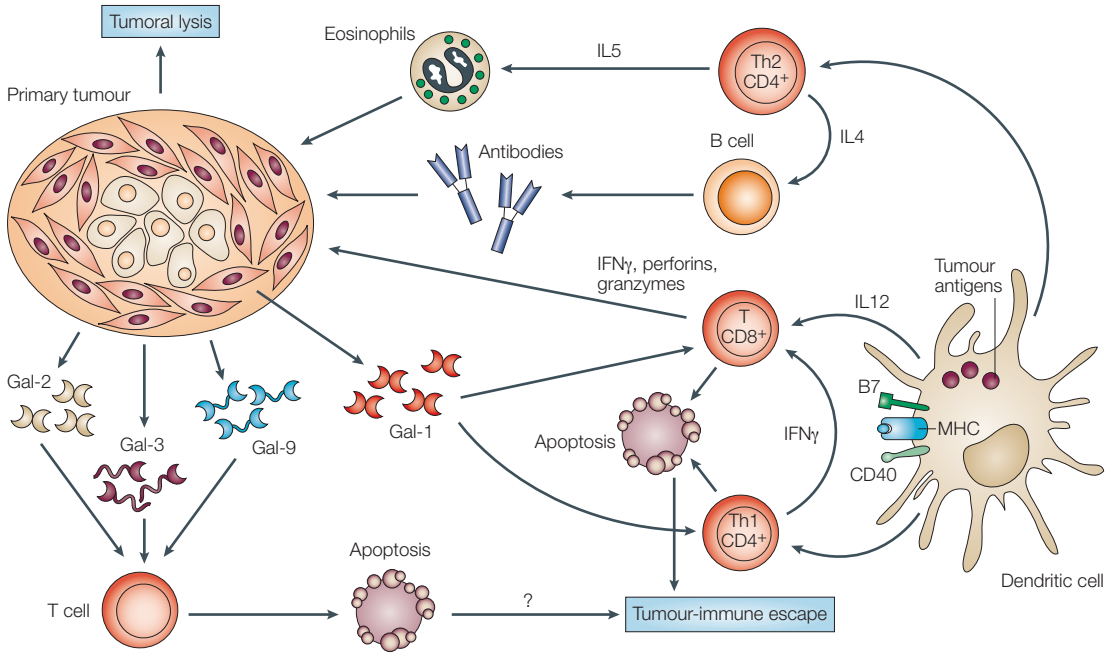

Figure 6 | **Anti-tumour immune responses and galectin-mediated escape mechanisms.** Immune responses can be categorized into two general types: cellular (involving CD8+ and CD4+ T-helper (Th) cell type 1 cells) and humoral (involving CD4+ Th2 and B cells) immune responses, which may impact tumour growth in several ways. Tumour-specific CD8+ T cells (T CD8+) are activated by the release of interleukin 12 (IL12) by antigen presenting dendritic cells, which express B7 and CD40 (co-stimulatory molecules required for T-cell activation). These activated CD8+ T cells can kill tumour cells directly. One subset of CD4+ T cells (Th1 CD4+), promotes the activation of CD8+ T cells through their secreted interferon γ (IFNγ). The other CD4+ T cell subset, (Th2 CD4+) stimulates an antibody-mediated immune response and activates B cells by releasing IL4. Th2 cells suppress Th1 responses and activates eosinophils by releasing IL5. CD8+ and CD4+ T cells secrete IFNγ, a Th1 cytokine, which can sensitize tumour cells to CD8+ T cells and activate other immune cells, thereby favoring tumour destruction. T cells use two main mechanisms to kill tumour cells: the death receptor pathway and the granule exocytosis pathway, which involves the secretion of perforin and granzymes. Tumours can evade immune responses by secreting immunosuppressive cytokines and soluble inhibitory factors, including galectin-1 (Gal-1). Gal-1 contributes to immune evasion by inducing apoptosis in effector T cells. Other galectins, including Gal-2, Gal-3 and Gal-9, also induce T-cell apoptosis, although their contributions to tumour-immune escape *in vivo* have not yet been demonstrated.

in vitro and *in vivo* experiments using transfectants expressing different amounts of galectin-1, we have demonstrated a link between galectin-1-mediated immunoregulation and tumour-immune escape. Our results demonstrate that tumours can overwhelm T-cell effector functions through the galectin-1-dependent modulation of effector T-cell survival[118]. Blocking the inhibitory effects of galectin-1 within tumour tissue results in reduced tumour mass and enhanced tumour rejection in a syngeneic model of murine melanoma. These effects are accompanied by the generation of a potent tumour-specific T-cell-mediated response.

Galectin-1 can also affect cell types other than T cells (reviewed in REFS 101,106). For example, it inhibits the release of inflammatory mediators from neutrophils and reduces the transendothelial migration of these cells in response to inflammatory stimuli[119,120].

Galectins 2, 3, 4 and 9. Other galectins can also regulate the immune and inflammatory responses (FIG. 5). Galectin-3 induces the activation of various inflammatory cell types (reviewed in REF. 97) and can function like a chemokine, attracting MONOCYTES and macrophages[121]. In agreement with these *in vitro* results, galectin-3-deficient mice exhibit significantly reduced inflammatory responses in models of peritoneal inflammation[51,122] and airway inflammation[123]. However, galectin-3 can induce T-cell apoptosis[124] and can restrict T-cell receptor (TCR)-initiated signal transduction by forming multivalent complexes with glycans present on the TCR[125]. The latter effect restrains the lateral mobility of the TCR complex, which is crucial for T-cell activation, thereby downregulating the T-cell response. In addition, galectin-3 might also reduce the immune response under certain circumstances by downregulating IL5 production[126] and blocking the differentiation of B lymphocytes into PLASMA CELLS, with the consequent reduction of specific antibodies[127]. Galectin-2 can induce T-cell apoptosis[128] and control the secretion of lymphotoxin-α by macrophages[129], and galectin-4 activates CD4+ T cells[130]. Finally, galectin-9 can also induce T-cell apoptosis[131,132] and function as an eosinophil chemoattractant[133]. Therefore, different galectins vary in their ability to stimulate or suppress the development of an effector immune response. Further studies are needed in order to fully understand the combined and/or redundant effects of galectins *in vivo*.

MONOCYTES
Circulating white blood cells that represent about 5% of total blood leukocytes. These cells can migrate into tissues to become macrophages.

PLASMA CELL
Terminally differentiated B lymphocyte. Plasma cells are the main antibody-secreting cells of the body. They are found in the medulla of the lymph nodes, in the spleen and in bone marrow.

Conclusions and future perspectives

Galectins can contribute to tumour progression through many different mechanisms. Most studies have focused on selected galectins, particularly galectin-1 and galectin-3. However, existing data indicate that other galectins, especially those whose expression is altered in cancer, probably contribute to various steps in tumour progression, and their functions warrant further *in vitro* and *in vivo* investigation. Even though the targeted disruption of galectin genes in mice does not result in overt phenotypic abnormalities, these mice do exhibit subtle but complex alterations during development[134]. In addition, detailed examination of these mice has revealed significant cellular abnormalities in specific experimental conditions. Therefore, experimental evidence does not support functional redundancy among galectins, and different galectins probably have discrete yet complementary roles in the regulation of tumour progression.

A better understanding of the role of galectins in cancer might lead to novel clinical applications — for diagnoses, predicting prognoses and developing new treatments. In fact, some progress has already been made in this direction. Galectins are frequently overexpressed in various human solid tumours and blood malignancies with respect to normal tissues, and some galectins function as diagnostic markers of specific cancers. In addition, altered expression of galectins correlates with the progression of certain tumours, and the expression levels of some galectins seem to have a prognostic value (reviewed in REFS 16,17,135).

Galectins have also emerged as promising molecular targets for cancer therapy, and galectin inhibitors have the potential to be used as anti-tumour and anti-metastatic agents. In fact, the galectin-3 C-terminal domain fragment significantly suppresses tumour growth and inhibits metastasis in a mouse model of human breast cancer[136]. In addition, peptides specific to the galectin-3 CRD significantly inhibit the adhesion of a human breast carcinoma cell line to endothelial cells *in vitro*[137]. Challenges for the future will be to employ potent and selective small inhibitors of galectins and, in fact, molecules with such properties have already been developed[138,139]. For some tumours, however, especially those that have downregulated expression of certain galectins (for example, galectin-7), introducing galectins by gene therapy or by specific induction of the gene might prove to be an effective therapy. In this regard, galectin expression can be modulated by differentiating, chemotherapeutic and antimetastatic agents, as shown for galectin-1 (REFS. 140,141). Increased understanding of the role of galectins in cancer should provide more insights into how the regulation of galectin expression or activity can be exploited for therapeutic purposes.

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Acknowledgements

We thank members of our laboratories for stimulating discussions and helpful suggestions, in particular D. Hsu, I. Kuwabara, J. Newman, and R.-Y. Yang (in F.-T.L.'s laboratory) and M. A. Toscano, J. M. Ilarregui, N. Rubinstein, and G. A. Bianco (in G.A.R.'s laboratory). We apologize to the authors of many relevant studies not cited because of space limitations. Work in authors' laboratories was supported by grants from the National Institutes of Health to F.-T.L. and by grants from Sales Foundation, Antorchas Foundation, Ministry of Health (Becas 'Carrillo-Oñativia'), Wellcome Trust, and University of Buenos Aires to G.A.R. G.A.R. is a member of CONICET.

Competing interests statement

The authors declare no competing financial interests.

Online links

DATABASES

The following terms in this article are linked online to:
Entrez Protein: BCL2 | galectin-1 | galectin-2 | galectin-3 | galectin-4 | galectin-7 | galectin-8 | galectin-9 | galectin-12 | HRAS | KIP1 | KRAS | NRAS | RAF1 | Synexin | TTF1 | WAF1

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