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Review

Regulated expression of galectin-3, a multifunctional glycan-binding protein, in haematopoietic and non-haematopoietic tissues

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Summary. Galectin-3 belongs to a family of highly conserved animal lectins characterized by their ability to recognize multiple N-acetyllactosamine sequences, which can be displayed on both N- and O-glycans on cell surface glycoconjugates. Although first identified in macrophages, galectin-3 (also called 'Mac-2, εBP, CBP35 or L-29') has been found to be widely distributed in several tissues and developmental stages where, depending on its extracellular or intracellular localization, it can display a broad diversity of biological functions including immunomodulation, host-pathogen interactions, embryogenesis, angiogenesis, cell migration, wound healing and apoptosis. In spite of the existence of several reviews describing the multifunctional properties of galectin-3, an integrated view of the regulated expression of this glycan-binding protein in different normal tissues is lacking. Here we attempt to summarize and integrate available information on galectin-3 distribution in normal haematopoietic and non-haematopoietic tissues, mainly in adulthood, with only a brief reference to its expression during embryonic stages. In addition, given the multiplicity of biological roles attributed to this protein, a brief description of galectin-3 functions is also included. Understanding how galectin-3 is regulated in normal tissues will contribute to a rational design of approaches aimed at modulating galectin-3 expression and subcellular localization for experimental and therapeutic purposes.

Key words: Galectin-3, Physiological expression, Normal tissue

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Introduction

Lectins represent a unique group of structurally diverse glycan-binding proteins which are endowed with the capacity to decipher biological information encoded by saccharide structures in a wide range of glycoconjugates (Sharon and Lis, 1989). Galectins, a family of highly conserved animal lectins that recognize ß-galactoside structures, are an ancient group of lectins which have attracted particular attention given their broad functional activity either inside or outside the cells. Galectins are characterized by their ability to recognize N-acetyllactosamine sequences, which can be displayed on both *N*- and *O*-glycans on cell surface glycoconjugates (Barondes et al., 1994a,b). All galectins contain conserved carbohydrate-recognition domains (CRDs) that are responsible for carbohydrate binding (Kasai and Hirabayashi, 1996; Cooper, 2002). So far, 15 mammalian galectins have been identified, which can be subdivided into three groups: those containing one CRD (galectin-1, -2, -5, -7, -10, -11, -13, -14, -15), those containing two distinct CRDs in tandem (galectin-4, -6, -8, -9, -12) and galectin-3, which consists of unusual tandem repeats stretches fused onto the CRD [reviewed in (Liu and Rabinovich, 2005)]. Different galectins are specific for different carbohydrate ligands, as they differ in their ability to accommodate certain saccharides attached to galactose and can form ordered arrays of complexes when they bind to multivalent glycoconjugates (Hirabayashi et al., 2002; Liu and Rabinovich, 2005). As galectins can bind either bivalently or multivalently, they can cross-link cell surface glycoconjugates, which, like many other receptor–ligand systems, can trigger a cascade of transmembrane signaling events (Brewer, 2002; Brewer et al., 2002; Liu and Rabinovich, 2005). Through this mechanism, galectins can modulate a wide variety of biological processes, including apoptosis, activation, cell

adhesion and cytokine secretion (Rabinovich et al., 2002).

Undoubtedly, the best studied member of the galectin family is the 'chimera-type' galectin-3, originally identified as the macrophage-associated molecule Mac-2 (Ho and Springer, 1982; Cherayil et al., 1989), a ubiquitously distributed protein responsible for multiple biological functions. Although first discovered in macrophages, galectin-3 has been found to be widely distributed in several tissues and developmental stages (Dumic et al., 2006; Yang et al., 2008).

The structure of galectin-3 appears to be unique among galectin family members; its single polypeptide chain forms two structurally distinct domains: (a) an amino terminal domain primarily containing tandem repeats of a conserved sequence of nine amino acids, Tyr-Pro-Gly-(Pro/G1n)-(Ala/Thr)-(Pro/Ala)-Pro-Gly-Ala; and (b) a carboxy terminal domain containing sequences shared by other S-type carbohydrate recognition domains (Albrandt et al., 1987; Robertson et al., 1990). This unique structure has shed light on the possible molecular mechanisms involved in its activities. Indeed, while soluble galectin-3 is monovalent in the absence of ligands, this glycan-binding protein can oligomerize through the N-terminal domain upon ligand recognition by its C-terminal CRD (Ahmad et al., 2004a). This oligomerization leads to cross-linking of ligands on the cell surface (Nieminen et al., 2007), which is essential for the majority of galectin-3 functions, including cell activation and cell adhesion [reviewed in (Rabinovich et al., 2002; Almkvist and Karlsson, 2004; Sato and Nieminen, 2004; Yang et al., 2008)]. Galectin-3 oligomerization on the cell surface has been linked to cell activation signals, likely resulting from receptor clustering events (Fernandez et al., 2005; Nieminen et al., 2005, 2007).

The N-terminal domain of galectin-3, a relatively flexible structure, is responsible for the formation of multimers and shows a positive cooperativity in lectin binding (Massa et al., 1993); this effect is biologically regulated through selective proteolysis by certain matrix metalloproteinases, such as MMP-2 and MMP-9 (Ochieng et al., 1998). Although the N-terminus lacks carbohydrate-binding activity, it participates together with the CRD in glycan recogniton (Barboni et al., 2000). The CRD of galectin-3 forms a globular structure, which accommodates the whole carbohydrate-binding site, thus being responsible for lectin activity of this protein (Dumic et al., 2006; Nieminen et al., 2008). It displays an identical topology and similar three-dimensional structure to that reported for the CRDs of homodimeric galectin-1 and -2, sharing with them 20–25% sequence identity. Like galectin-1 and -2, it is composed of 5-stranded (F1–F5) and 6-stranded (S1–S6a/6b) ß-sheets which associate in a ß-sandwich arrangement (Seetharaman et al., 1998). The x-ray crystal structure of the human galectin-3 CRD, in complex with lactose and N-acetyllactosamine, was described in detail at 2.1-Å resolution (Seetharaman et al., 1998). In addition, experiments using nuclear magnetic resonance analysis suggested possible interactions between portions of the N-terminal domain and the CRD of galectin-3 (Birdsall et al., 2001).

The carbohydrate-binding specificity of galectin-3 is similar to that of galectin-1 in that both of them bind to LacNAc sequences and lactose residues (Barondes et al., 1994b; Kasai and Hirabayashi, 1996; Gabius, 1997). Some differences exist, however, since galectin-3 binds not only to terminal but also to internal LacNAc residues in polylactosamine chains, whereas galectin-1 recognizes mainly non-reducing terminal LacNAc residues (Ahmad et al., 2004b). Detailed information on oligosaccharide specificity of galectin-3 is carefully discussed by Hirabayashi and colleagues (2002).

The interaction of galectin-3 or its CRD with carbohydrate ligands is accompanied by rearrangement of the backbone protein loops near the binding site (Umemoto et al., 2003). Interestingly, galectin-3 can undergo phosphorylation, mainly at position Ser^{6} and also at Ser^{12}, which strongly affects its sugar-binding affinity (Mazurek et al., 2000), and many biological functions [reviewed in (Dumic et al., 2006)]. Indeed, phosphorylation at Ser^{6} was proposed to be an "on/off" switch of its downstream biological effects (Mazurek et al., 2000).

In spite of the great number of studies dealing with the complex diversity of galectin-3 structural, biochemical and functional properties, little information is available regarding its tissue distribution and expression pattern in normal murine and/or human tissues. Given the involvement of this glycan-binding protein in an assortment of intracellular and extracellular processes (Fig. 1), this review attempts to summarize the regulated expression and distribution of galectin-3 in normal haematopoietic and non-haematopoietic murine and human tissues (Table 1), mainly in adulthood, but also making a brief reference to embryonic stages. In addition, given the wide diversity of biological functions attributed to this endogenous lectin, a summarized description of galectin-3 functions is also provided.

General functions of galectin-3

Galectins have been detected in a wide variety of cells and tissues where they can regulate different biological processes, thus making this protein family an attractive target in biomedicine (Yang et al., 2008). The biological functions of galectin-3 are defined by its selective intracellular or extracellular localization. In fact, this lectin has been proposed to shuttle between the cytoplasm and nucleus on the basis of targeting signals that are recognized by importins for nuclear localization and exportin-1 (CRM1) for nuclear export. Depending on the cell type, specific *in vitro* experimental conditions, or tissue location, galectin-3 has been reported to be exclusively cytoplasmic, predominantly nuclear, or distributed between the two compartments (Haudek et al., 2010). Cytosolic galectin-3 was found to

be involved in the regulation of cell proliferation, differentiation and survival through specific interactions with the oncogene K-Ras or the phosphoinositide 3 kinase (PI3K)-Akt signaling pathway [reviewed in (Dumic et al., 2006)]. In addition, several cytosolic proteins involved in the regulation of apoptosis have been identified as specific galectin-3-binding partners, including Bcl-2, CD95 (APO-1/Fas), and nucling (Yang et al., 1996; Fukumori et al., 2004; Liu et al., 2004). On the other hand, nuclear expression of galectin-3 has been associated with the regulation of gene transcription. By enhancing or stabilizing transcription factor binding to the CRE and SP1 consensus sites in the cyclin D1 promoter region, galectin-3 can induce cyclin D1 promoter activity (Lin et al., 2002). In addition, this lectin was found to be associated with ribonucleoprotein complexes (Laing and Wang, 1988) and to act as a pre-mRNA splicing factor (Dagher et al., 1995). Furthermore, galectin-3 plays an important role in the regulation of Wnt/ß-catenin signaling route, which is a key pathway in development, tissue homeostasis, and tumor growth, though the precise mechanism underlying these effects still remains unclear. Shimura and colleagues (2004) found that galectin-3 binds to the ß-catenin/TCF complex, co-localizes with ß-catenin in the nucleus, and induces transcriptional activity of TCF4 in breast cancer cells. However, while regulation of ß-catenin nuclear accumulation and activation of Wnt signaling by galectin-3 was confirmed in a recent work, the authors were unable to detect a similar direct interaction between galectin-3 and ß-catenin (Song et al., 2009). The biological functions of galectin-3 in the

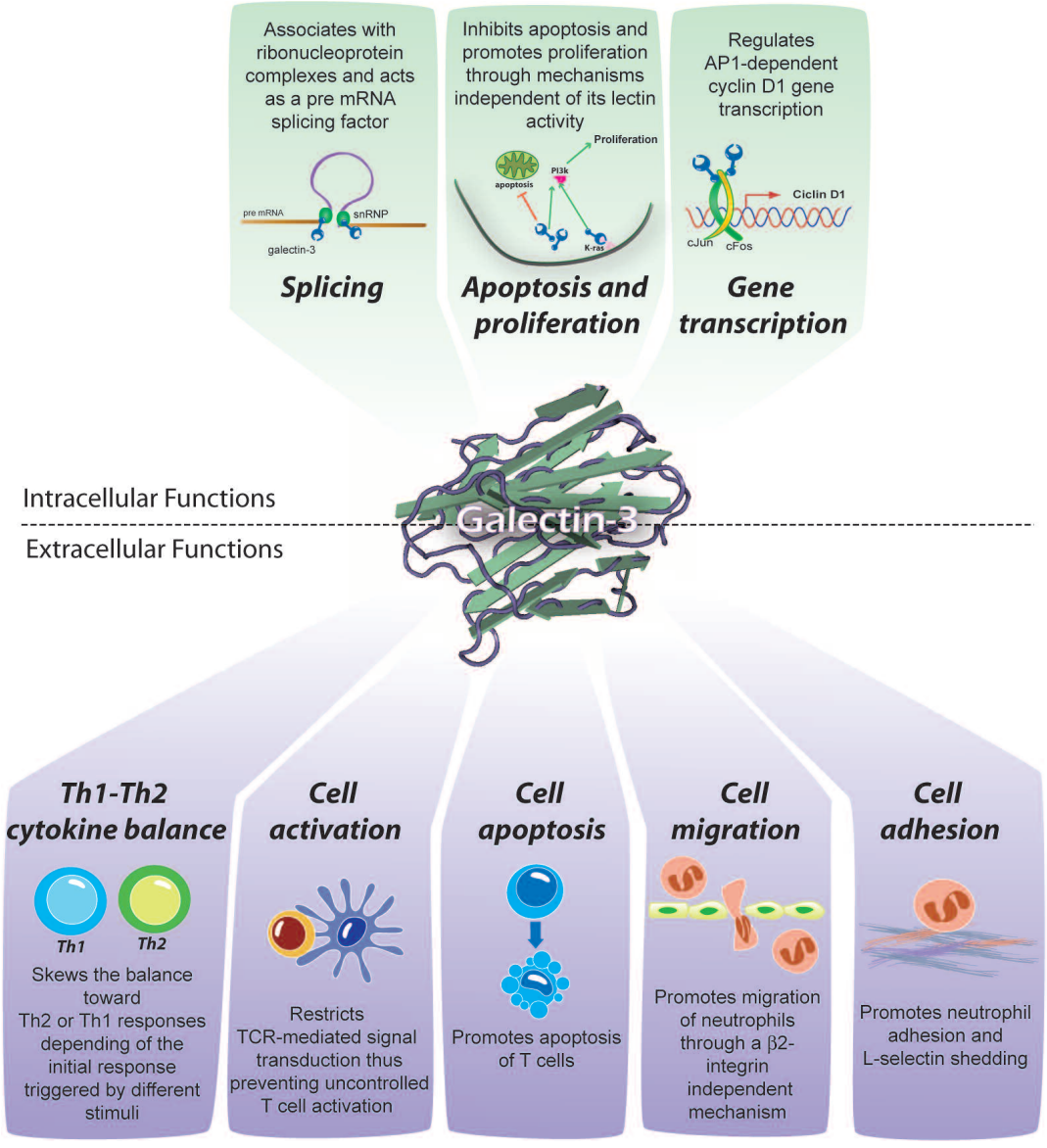

Figure 1. Intracellular and extracellular functions of galectin-3. The figure illustrates selected examples of the intracellular and extracellular functions of galectin-3. This 'chimera-type' lectin controls intracellular processes, including cell cycle progression, viability and gene expression, mostly through protein-protein interactions. Extracellularly, galectin-3 interacts with specific glyco-receptors (i.e.. glycoproteins or glycolipids) and triggers different biological processes, including cellular activation, differentiation, cytokine synthesis, cell adhesion and migration and apoptosis. Abbreviations: PI3K: phosphoinositol 3-kinase ; RNP: ribonucleoproteins ; TCR: T cell receptor; Th1: T helper 1, Th2: T helper 2.

nucleus are reviewed in detail by Patterson and colleagues (2004).

Notably, although galectin-3, as well as other vertebrate galectins, lacks recognizable secretion signal sequences (Hughes, 1999), the extracellular localization of this protein is now undisputed. This glycan-binding protein may be associated to the cell surface or localized within the extracellular matrix, either bound to its numerous extracellular counterparts or present in the circulation and in biological fluids (Dabelic et al., 2006; Dumic et al., 2006). Extracellular galectin-3 exhibits numerous autocrine and paracrine effects. It mediates cell adhesion and cell activation, and acts as a chemoattractant for certain cell types, modulating various biological processes such as maintenance of cellular homeostasis, immune reactions, organogenesis and angiogenesis, tumor cell invasion and metastasis [reviewed in (Hsu and Liu, 2004; Ochieng et al., 2004; Takenaka et al., 2004; van den Brule et al., 2004; Liu and Rabinovich, 2005)]. Notably, galectin-3-deficient (*Lgals3*$^{-/-}$) mice display several important phenotypes, although it is not clear whether they reflect intracellular or extracellular functions of this protein (Yang et al., 2008).

Immunomodulatory functions of galectin-3

During the past decade, compelling evidence has been accumulated regarding the ability of galectins to modulate a wide variety of immunological processes (Bianco et al., 2006). While galectin-1 is generally regarded as a negative regulator of inflammatory and autoimmune responses *in vivo* (Rabinovich et al., 2002), the role of galectin-3 in inflammatory disorders is less clear. Galectin-3 expression is increased in inflammatory tissues in patients with inflammatory ocular diseases (Hrdlickova-Cela et al., 2001), rheumatoid arthritis (Harjacek et al., 2001; Ohshima et al., 2003) and atherosclerosis (Nachtigal et al., 1998). In addition, studies on *Lgals3*$^{-/-}$ mice have provided strong support for a role of galectin-3 in sustaining inflammatory responses. Targeted disruption of galectin-3 gene in mice results in a reduced inflammatory response after induction of peritonitis, compared to *wild-type* animals (Hsu et al., 2000). In addition, galectin-3 deficiency has led to reduced inflammation during pneumococcal pneumonia (Nieminen et al., 2008), atherosclerosis (Nachtigal et al., 2008) and inflammatory bowel disease (Jawhara et al., 2008). However, it has been previously shown that genetic delivery of galectin-3 suppresses airway inflammation in a rat asthma model (del Pozo et al., 2002). Also, *Lgals3*$^{-/-}$ mice were reported to develop higher inflammatory responses in the lung following infection with the protozoan parasite *Toxoplasma gondii* (Bernardes et al., 2006). Given these apparently constrasting effects, we might speculate that pro-inflammatory or anti-inflammatory effects of galectin-3 might depend on its particular tissue distribution, with different concentrations attained by the endogenously-regulated lectin or the exogenously-administered protein or it might be associated to different pathological conditions.

In the central nervous system (CNS), galectin-3 is highly up-regulated in prion-infected brain tissue, where it seems to play a detrimental role (Mok et al., 2007). Also, an essential role for galectin-3 has been

Table 1. Selective distribution of galectin-3 in murine and human non-haematopoietic tissues: An overview.

Tissue	Mouse		Human	
	Cell type	Ref.	Cell type	Ref.
Respiratory tract	Covering bronchiolar epithelium.	Kim et al., 2007	Bronchial epithelial cells and chondrocytes of the bronchial cartilage.	Mathieu et al., 2005.
	Lung resident macrophages.	Kim et al., 2007; Sato et al., 2002; Kasper and Hughes 1996.	Alveolar macrophages.	Mathieu et al., 2005.
Digestive Tract	Epithelial cells of the stomach, small intestine and large intestine.	Nio et al., 2005; Kim et al., 2007.	Gastric epithelial cells.	Fowler et al., 2006.
	Tissue resident macrophages of the lamina propria.	Kim et al., 2007.	Colonic epithelial cells and intestinal macrophages.	Muller et al 2006; Lippert et al., 2008; Mercer et al., 2009.
Reproductive Tract	Ovarian luteal cells and stromal macrophages but not growing follicles.	Kim et al., 2007.	Endometrium epithelial glandular cells and decidua.	von Wolff et al., 2005.
			Ovarian surface epithelium.	Devouassoux-Shisheboran et al., 2006.
	Uterine covering endometrial epithelium and connective tissue macrophages	Kim et al., 2007.	All Sertoli cells and few Leydig cells of post-pubertal normal testicular parenchyma.	Devouassoux-Shisheboran et al., 2006.
Urinary Tract	Renal cortex and medulla.	Nio et al., 2006; Kim et al., 2007.	Kidney tubular epithelial cells and glomerular cells.	Kang et al., 2009; Merseburger et al., 2008a.
	Transitional epithelium from the renal pelvis to the urethra.	Nio et al., 2006.		

demonstrated in the promotion of autoimmune brain inflammation (Jiang et al., 2009). In this regard, *Lgals3*$^{-/-}$ mice developed markedly reduced signs of demyelination and T helper (Th)-17-mediated autoimmune pathology. Also, *Lgals3*$^{-/-}$ mice exhibited reduced macrophage infiltration in the CNS, supporting a key role for this lectin in promoting inflammation via local recruitment of leukocytes and promotion of Th17 responses (Jiang et al., 2009). In fact, the notion that galectin-3 induces chemotaxis of monocytes and macrophages was clearly demonstrated using *in vitro* and *in vivo* approaches (Hsu et al., 2000; Sano et al., 2000).

So far, most *in vitro* and *in vivo* studies support the notion that galectin-3 mainly triggers or amplifies inflammatory responses by promoting immune cell activation, migration and pro-inflammatory cytokine secretion, or by suppressing T cell apoptosis (Rabinovich et al., 2007). The molecular mechanisms underlying these effects are analyzed in the following section. In addition, the importance of galectin-3 in triggering innate and adaptive immune response may

Table 2. Regulated expression of galectin-3 in murine and human haematopoyetic tissues: An overview.

		Murine galectin-3		Human galectin-3	
		Expression	Ref.	Expression	Ref.
A. Cell type	Monocytes and Macrophages	Tissue resident macrophages of most organs.	Kim et al., 2007.	Expressed in normal peripheral blood monocytes. *In vitro*, expression correlates with the differentiation of macrophages.	Liu et al., 2005
		Expression correlates with maturation.	Leenen et al., 1986.		
		Activating stimuli (calcium ionophore, IL-4 and IL-13) induce its expression while others (LPS, INF-≥) have inhibitory effects.	MacKinnon et al., 2008; Sato and Hughes, 1994.		
	Dendritic cells (DCs)	Present in the cytoplasm of bone-marrow derived immature DCs. Expression increases during DC maturation.	Hsu et al., 2009.	More abundantly expressed in immature than in mature DCs.	Dietz et al., 2000.
		Mature DCs.	Breuilh et al., 2007.		
	Neutrophils	Low levels of endogenous galectin-3.	Farnworth et al., 2008.	Present in neutrophils from normal donors and patients with inflammatory disorders.	Trough et al., 1993a.
	Mast cells	Bone-marrow-derived mast cells and mast cell lines.	Frigeri and Liu 1992.	Human mast cells of several organs, in nuclear heterochromatin and cytoplasmic secretory granules.	Craig et al., 1995.
		Secreted upon activation by FcμRI cross-linkage.	Chen et al., 2006		
	Lymphocytes	Absent or only sparsely expressed in resting lymphocytes and lymphoid cell lines.	Joo et al., 2001; Dumic et al., 2006.	Almost undetectable in human T cell lines.	Hsu et al., 1996; Fukumori et al., 2003.
		Strongly expressed upon T cell activation.	Joo et al., 2001.	Low levels in isolated human peripheral blood lymphocytes.	Hsu et al., 1996.
		Strongly expressed upon B cell activation.	Acosta-Rodriguez et al., 2004.		
B. Lymph Organ	Spleen	Highly expressed in the red pulp, where DCs and macrophages are the most abundant cells. Poorly expressed in the white pulp, which is mainly composed by T and B resting lymphocytes.	Kim et al., 2007.	No information available or recorded.	-
	Thymus	Detected mainly in the medulla and to a lesser extent in the cortex. Produced by epithelial and phagocytic cells.	Villa-Verde et al., 2002; Silva Monteiro et al., 2007	Detected around thymocytes and abundantly expressed within epithelial cells in both cortical and medullar regions.	Stillman et al., 2006.
				Expressed in Hassal´s corpuscles and interstitial macrophages.	D´Haene et al., 2005.
	Lymph nodes	No data available or recorded.	-	Detected in follicular DCs and in interdigitating cells.	D´Haene et al., 2005; Stillman et al., 2006.
				Expressed in stroma surrounding small vessels, but not in endothelial cells of extrafollicular regions.	Stillman et al., 2006.
				Found in macrophages and endothelial cells of extrafollicular regions.	D´Haene et al., 2005.

also emerge from the ability of this lectin to recognize ß-galactoside-containing glycoconjugates on pathogen surfaces. Galectin-3 can bind bacterial lipopolysaccharides (LPS) via two distinct sites: through its CRD by interacting with ß-galactoside containing side-chains in a lactose-dependent manner, and through its N-terminal domain by interacting with a non-glycan structure, lipid A/inner core region of LPS, independently of its lectin activity (Mey et al., 1996). Through these interactions, galectin-3 contributes to complex molecular mechanisms by which the host innate immune system recognizes infectious agents and drives pro-inflammatory responses (Sato and Nieminen, 2004).

Molecular mechanisms underlying the immunoregulatory activities of galectin-3

Galectin-3 can act in a dual manner either protecting cells from apoptosis or stimulating cell death, depending on whether the protein acts within the intracellular or the extracellular compartment (Yang et al., 1996; Fukumori et al., 2003; Stillman et al., 2006). In this regard, Yang and colleagues (1996) demonstrated that T-cell transfectants overexpressing galectin-3 are protected from apoptosis induced by a variety of agents including Fas ligand and staurosporine. The anti-apoptotic effect of endogenous galectin-3 was also demonstrated in B lymphoma cell lines (Hoyer et al., 2004) and macrophages (Hsu et al., 2000). A large body of evidence suggests that endogenous galectin-3 may confer resistance to apoptosis by engaging apoptosis-regulation pathways inside the cells (Liu et al., 2002; Hsu et al., 2006) or by modulating mitochondrial homeostasis (Matarrese et al., 2000). In contrast, extracellular galectin-3 has been shown to induce apoptosis of T cells (Stillman et al., 2006), through mechanisms that involve caspase-3, but not caspase-8 activation (Fukumori et al., 2003). In one study, CD7 and CD29 were proposed to mediate galectin-3–induced T cell apoptosis (Fukumori et al., 2003), while other studies demonstrated that CD45 and CD71, but not CD29 and CD43 are involved in this function (Stillman et al., 2006). *In vitro* treatment with exogenous galectin-3 also induces apoptosis in polymorphonuclear neutrophils, although the specific receptors in this cell type have not yet been identified (Fernandez et al., 2005). Furthermore, recent evidence suggests a functional cross-talk between intracellular and extracellular galectins in the regulation of T-cell death. Hahn and colleagues (2004) found that galectin-1-induced cell death is inhibited by intracellular expression of galectin-3, demonstrating how different members of the galectin family might act in concert to modulate T-cell survival and regulate the inflammatory response.

In addition to the regulation of apoptosis, cell proliferation has also been shown to be regulated by galectin-3. The function of endogenous galectin-3 as a positive growth regulator of T cells was established by demonstrating that cells treated with galectin-3-specific antisense oligonucleotides had reduced proliferation (Joo et al., 2001). In contrast, exogenously added galectin-3 appears to have a negative effect on T cell growth, as it inhibits mitogen-induced proliferation of peripheral blood T cells (Muller et al., 2006).

Galectin-3 can also modulate T-cell activation. Demetriou and colleagues (2001) found that this lectin might play a role in restricting TCR complex-initiated signal transduction. This endogenous lectin appears to form multivalent complexes with N-glycans on the TCR, which potentially restrict the lateral mobility of TCR complexes and raise the threshold for ligand-dependent receptor clustering and signal transduction, thus preventing uncontrolled activation of T cells (Demetriou et al., 2001). A further mechanistic analysis revealed that N-glycan branching coordinates homeostatic set-points in T-cell activation and signaling. When galectin-3-N-glycan lattices are disrupted, T cell hyperactivity and autoimmunity occur, suggesting a critical function of glycosylated structures in regulating T cell homeostasis (Grigorian et al., 2007). Recent evidence further demonstrated that endogenous galectin-3 can directly control T cell activation at sites of immunological synapse (Chen et al., 2009).

It is well established that, in different autoimmune, allergic and inflammatory conditions, the Th1/Th2 cytokine balance may be differentially modulated by galectin-glycan interactions (Bianco et al., 2006). While galectin-1 skews the balance toward a Th2-polarized cytokine profile characterized by increased interleukin (IL)-5 and IL-10 production (Rabinovich et al., 2002; Rabinovich and Toscano, 2009), exogenous galectin-3 can down-regulate IL-5 synthesis when targeted to inflammatory sites (Cortegano et al., 1998; del Pozo et al., 2002; Lopez et al., 2006) and silence Th2-mediated chronic and acute airway inflammation (del Pozo et al., 2002; Lopez et al., 2006). However, *Lgals3*$^{-/-}$ mice paradoxically develop higher Th1 responses (Zuberi et al., 2004). These discrepancies may reflect opposite effects of endogenous versus exogenous galectin-3 in the regulation of pro-inflammatory cytokines or may be due to different concentrations attained *in vivo* by the endogenously-regulated lectin versus those achieved by gene or protein therapy. Moreover, in a setting of pathogen infection, Breuilh and colleagues (2007) challenged *Lgals3*$^{-/-}$ mice with Schistosoma mansoni, a parasite characterized by an intrinsic ability to tailor immune responses toward Th2-polarized profiles. Interestingly, *Lgals3*$^{-/-}$ mice infected with this parasite developed a skewed Th1 response compared with their wild-type counterpart (Breuilh et al., 2007). However, during an experimental model of *Paracoccidioides brasiliensis* infection, mice lacking galectin-3 displayed a Th2-polarized response compared with their wild-type counterpart (Ruas et al., 2009). Thus, endogenous galectin-3 may differentially regulate the Th1/Th2 cytokine balance depending on the initial response triggered by different pathogens or distinct

immunological insults. In contrast to galectin-1, this effect does not seem to be associated with a differential susceptibility of T helper subsets to galectin-3-induced cell death (Toscano et al., 2007).

On the other hand, galectin-3 can affect inflammatory responses by modulating cell adhesion and migration of various immune cell types (Hughes, 2001). Recombinant galectin-3 was found to promote adhesion of human neutrophils to laminin (Kuwabara and Liu, 1996) and to endothelial cells (Sato et al., 2002). In fact, galectin-3 acts as an adhesion molecule for neutrophils through ligand cross-linking (Kuwabara and Liu, 1996; Sato et al., 2002; Nieminen et al., 2007) and favors neutrophil recruitment during *S. pneumoniae* lung infection through $ß_2$-integrin-independent mechanisms (Sato et al., 2002; Nieminen et al., 2008). In addition, endogenous galectin-3 facilitates adhesive interactions between T cells and dendritic cells (DCs) or macrophages (Swarte et al., 1998) and induces CD13-mediated homotypic aggregation of monocytes (Mina-Osorio et al., 2007). Alternatively, galectin-3 can also promote migration of human monocytes/macrophages (Sano et al., 2000) and induces IL-1 production by human monocytes (Liu et al., 1995). In naive and primed neutrophils galectin-3 favors L-selectin shedding and IL-8 production (Nieminen et al., 2005) and promotes neutrophil activation and degranulation (Fernandez et al., 2005), as well as the synthesis of reactive oxygen intermediates (Yamaoka et al., 1995; Almkvist et al., 2001).

The impact of endogenous galectin-3 in phagocytosis has been demonstrated by comparing macrophages from *Lgals3*$^{-/-}$ and *wild type mice* (Sano et al., 2003). *Lgals3*$^{-/-}$ macrophages were found to be defective in phagocytosis of opsonized erythrocytes and apoptotic thymocytes. Interestingly, intracellular galectin-3 was concentrated around phagosomes. On the other hand, studies of mast cells in *Lgals3*$^{-/-}$ mice revealed a critical role for intracellular galectin-3 in the regulation of mast cell function. Mast cells devoid of galectin-3 produced lower levels of granular mediators and cytokines when activated by cross-linkage of cell surface immunoglobulin (Ig)E receptor, compared with their wild type counterpart (Chen et al., 2006). Furthermore, the function of endogenous galectin- 3 in DC physiology has also been demonstrated as *Lgals3*$^{-/-}$ DCs secreted lower amounts of IL-12 than wild-type cells in response to microbial challenge (Bernardes et al., 2006). Thus, galectin-3 controls a broad spectrum of immunological functions, including cell adhesion, migration, activation, apoptosis and cytokine secretion within innate and adaptive immune compartments.

Expression of galectin-3 in murine tissues

Murine embryonic tissues

During mouse embryogenesis, galectin-3 is regulated in a spatio-temporal fashion. The onset of galectin expression occurs within the fourth day of gestation when this protein is detected in blastocyst trophectoderm cells (Poirier and Robertson, 1993). At day 8.5 of gestation, galectin-3 is exclusively expressed in notochord cells where it persists until this structure disappears (Fowlis et al., 1995). This lectin is subsequently expressed in the cartilage of vertebrae, ribs and facial bones and the suprabasal layer of epidermis, from day 13.5, suggesting a role in the establishment and/or maintenance of notochord as well as the formation of cartilage and differentiation of skin (Fowlis et al., 1995). Moreover, Colnot and colleagues (1999) showed the presence of galectin-3 in differentiated chondrocytes of the epiphyseal plate cartilage of long bones of both fetal and neonatal mice, and proposed a potential role for galectin-3 in the process of endochondral bone formation, possibly as a regulator of chondrocyte survival. At different stages of mouse development, galectin-3 is expressed by the endodermal lining of the bladder, larynx and oesophagus (Dumic et al., 2006), and is also present in embryonic macrophages (Fowlis et al., 1995).

Not only galectin-3 but also several other members of the galectin family have been proposed to be involved in developmental processes and embryogenesis (Colnot et al., 1996, 1999). However, a rigorous characterization of their specific roles in single knockout mice is still lacking probably due to functional redundancies among different members of the family. Given that the three major galectin subfamilies (proto-type, chimera-type and tandem repeat-type) are also present in teleost fish, and considering the remarkable advantages of using the zebrafish (*Danio rerio*) as a model organism, its use has been proposed as an alternative approach to study the regulated expression and functions of galectins during development (Vasta et al., 2004). The expression of zebrafish Drgal3, which exhibits the typical organization of mammalian galectin-3, has been carefully examined in order to characterize the diversity and developmental expression of the zebrafish galectin repertoire. The authors found that during embryogenesis the expression of Drgal3 is detected as soon as the fertilization process occurs and increases 3 h post-fertilization, suggesting an early developmental regulation of Drgal3 which differs substantially from that reported in the mouse (Ahmed et al., 2004).

Murine adulthood

Non-haematopoietic murine tissues

In a study aimed at analyzing the expression of galectins along the mouse digestive tract, expression of galectin-3 was detected by *in situ* hybridization exclusively in epithelial cells. Transcripts were abundant within the large intestine, including the cecum, colon, and rectum, whereas the stomach and small intestine showed weak signals that increased slightly toward the ileum (Nio et al., 2005). However, in a more recent

study, galectin-3 was detected by immunohistochemistry, not only in epithelial cells of the stomach, small intestine (ileum) and large intestine (colon), but also in adjacent cells -presumably tissue resident macrophages- in the lamina propria (Kim et al., 2007). Interestingly, among several murine tissues, the colon presented the highest level of galectin-3 expression, followed by the lung, spleen, stomach, uterus and ovary, as evaluated by immunohistochemistry and Western blot analysis (Kim et al., 2007). Regarding other digestive tract-associated organs, specific staining was detected in cells distributed along the liver sinusoids with the appearance of Kupffer cells, though no staining was detected in hepatocytes. In addition, a few galectin-3-positive cells were occasionally found in the interstitium of the pancreas, but not concentrated in exocrine or endocrine cells (Kim et al., 2007).

Hierarchically the lung appears to be the second among different murine tissues expressing the highest levels of galectin-3 (Kim et al., 2007). Galectin-3 immunoreactivity was described in the covering epithelia of the bronchioles, and in some resident macrophages (Kim et al., 2007). However, Sato and colleagues (2002) showed that in non-infected lungs, galectin-3 staining was scattered. In fact, the distribution and shape of labeled cells suggested that only resident alveolar macrophages were positive for galectin-3, consistent with previous reports (Kasper and Hughes, 1996). No significant galectin-3 positive staining was observed in uninfected alveolar wall. However, the content of galectin-3 remarkably increased during the progression of murine streptococcal pneumonia, and distributed in the vicinity of vascular and alveolar regions of infected lungs with a kinetic that closely paralleled the infiltration of neutrophils into the alveolar spaces (Sato et al., 2002). Interestingly, expression of galectin-3 was prominent in rat lung Clara cells and macrophages and was subjected to the control of endogenous glucocorticoids in a cell-specific manner (Maldonado et al, unpublished data).

The expression of galectin-3 in the murine reproductive tract was described in detail by Kim and colleagues (2007). In the ovary, galectin-3 showed intense immunostaining in luteal cells and in some stromal macrophages, but was not found in growing follicles. Considering the role of galectin-3 in cell survival, the authors postulated that this lectin may play a role in the maintenance or survival of luteal cells during pregnancy, and/or in protecting luteal cells from the surrounding environment, including immune cell attack. In the uterus, galectin-3 labeling was detected in some parts of the covering endometrial epithelium, as well as in macrophages in the loose connective tissues of the uterine mucosa (Kim et al., 2007). In view of the established roles of galectins in modulating immune responses and regulating tumor progression, their participation in modulating immune tolerance during implantation is warranted. In fact, recent findings demonstrated a pivotal role for galectin-1 in promoting fetomaternal tolerance and preventing fetal rejection (Blois et al., 2007). Whether galectin-3 plays similar or opposite roles in immune tolerance and pregnancy still remains to be investigated.

Galectin-3 is the major ß-galactoside-binding lectin expressed in the murine urinary system. By *in situ* hybridization and immunohistochemistry, galectin-3 was found to be continuously expressed from the kidney to the distal end of the urethra (Nio et al., 2006). Both the renal cortex and the medulla expressed high amounts of galectin-3 (Nio et al., 2006; Kim et al., 2007). Immunoreactivity was stronger in the cortical collecting ducts (Nio et al., 2006), but was scarcely detected in glomeruli and proximal and distal tubules in the cortex (Kim et al., 2007). All cell layers of the transitional epithelium from the renal pelvis to the urethra strongly expressed galectin-3 at the mRNA and protein levels. An electron microscopic study demonstrated diffuse cytoplasmic localization of galectin-3 in principal cells of the collecting ducts and in the bladder epithelial cells. Urethral galectin-3 expression at the pars spongiosa decreased in intensity near the external urethral orifice (Nio et al., 2006).

Scarce information is available regarding the expression of galectin-3 in murine heart, brain and adrenal gland. Galectin-3-bright round cells were occasionally found in the interstitial tissues of the heart, but cardiomyocytes were not found to be positive for this lectin (Kim et al., 2007). In the brain, galectin-3 was only scarcely detected in some ependymal cells of the cerebral ventricle, but not in neurons (Kim et al., 2007). Finally, galectin-3-positive cells were mainly detected in the adrenal medulla, but occasionally found in the adrenal cortex (Kim et al., 2007).

Haematopoietic murine tissues

Galectin-3 has been identified in almost all innate immune cells, including neutrophils, eosinophils, basophils, mast cells, DCs, and monocytes/macrophages from different tissues (Dumic et al., 2006). Indeed, Kim and colleagues (2007) described the expression of galectin-3 in tissue resident macrophages present at the loose connective tissues of most organs. Galectin-3 is highly expressed and secreted by macrophages, and its expression appears to correlate with maturation of these cells (Leenen et al., 1986). Sato and Hughes (1994) found that galectin-3 secretion is stimulated in macrophages by activating stimuli, including the calcium ionophore A23187, although its surface expression is markedly reduced upon activation of macrophages with bacterial LPS. Moreover, recent data suggest that alternative activation of macrophages with IL-4 and IL-13 stimulates galectin-3 expression and release, while classical macrophage activation by IFN-γ or LPS inhibits expression of this glycan-binding protein (MacKinnon et al., 2008). In fact, the divergent functions of galectin-3 in different disease models (see above) may reflect the dual role of this lectin within the

monocyte/macrophage compartment (MacKinnon et al., 2008).

In a recent study, Hsu and colleagues (2009) found variable amounts of intracellular galectin-3 during culture of immature bone marrow-derived DCs, but little or no galectin-3 on the cell surface. Of note, the levels of intracellular galectin-3 considerably increased on DCs subjected to maturation with LPS, a Toll-like receptor (TLR) 4-dependent stimulus. The study showed that galectin-3 is accumulated in membrane ruffles and lamellipodia in stimulated DCs, and revealed a function of endogenous galectin-3 in regulating DC motility both *in vitro* and *in vivo*. As mentioned above, in a murine model of schistosomiasis, Breuilh and colleagues (2007) found that endogenous galectin-3 does not intrinsically influence DC differentiation or maturation, while it determines the magnitude of adaptive immune responses. In contrast, endogenous galectin-1 plays a pivotal role in promoting the generation of tolerogenic DCs and initiating a tolerogenic circuit through mechanisms involving IL-27 and IL-10 (Ilarregui et al., 2009).

Although mouse neutrophils can be activated by galectin-3, they express very low levels of this endogenous lectin (Farnworth et al., 2008). Extracellular galectin-3, which is up-regulated in macrophages and other cell types of the surrounding microenvironment, induces neutrophil recruitment to infection sites and promotes their activation (see above). In addition, galectin-3 expression is detected not only in mast cell lines, but also in bone marrow-derived mouse mast cells (Frigeri and Liu, 1992). Chen and colleagues (2006) clearly demonstrated the relevance of endogenous galectin-3 in mast cell biology. Upon activation by FcεRI cross-linkage, *Lgals3*$^{-/-}$ mast cells secreted significantly lower amounts of histamine and IL-4, compared with wild-type mast cells. This effect was translated into significantly reduced passive cutaneous anaphylactic reactions in *Lgals3*$^{-/-}$ compared to wild-type mice.

In contrast to its broad cellular distribution in innate immune cells, galectin-3 is absent or only sparsely expressed in resting lymphocytes and in several lymphoid cell lines (Joo et al., 2001; Dumic et al., 2006). However, T cell activation through CD3 cross-linking or exposure to concanavalin A resulted in considerably enhanced galectin-3 expression, an effect which was potentiated by cytokines such as IL-2, IL-4 and IL-7 (Joo et al., 2001). Moreover, activation of B lymphocytes with IL-4 and/or CD40 cross-linking resulted in increased galectin-3 expression, which contributed to facilitate the survival of B cells and promoted the differentiation toward a memory B cell phenotype (Acosta-Rodriguez et al., 2004).

By means of immunohistochemical analysis, the expression of galectin-3 in the spleen was found to be much higher in the red pulp than that in the white pulp (Kim et al., 2007). This local expression may reflect the selective distribution of immune cells in this organ, in which the majority of resident macrophages and DCs localize in the red pulp, whereas T and B lymphocytes are present in the white pulp. Importantly, naïve splenic lymphocytes express only trace amounts of galectin-3, which could not be detected by immunohistochemistry but may increase upon T cell activation (Kim et al., 2007).

Finally, galectin-3 is abundant in the thymus, where it modulates carbohydrate-dependent thymocyte interactions within the thymic microenvironment. This endogenous lectin is found mainly in the medulla and to a lesser extent in the cortex of young adult mouse thymus. Distinct microenvironmental components, such as thymic epithelial cells, thymic nurse complexes and phagocytic cells of the thymic reticulum, produce, secrete and accumulate high amounts of galectin-3 on the cell surface, which contributes to modulate thymocyte migration and survival (Villa-Verde et al., 2002; Silva-Monteiro et al., 2007).

Expression of galectin-3 in human tissues

Human embryonic period

Compared to the mouse, knowledge on the role of galectin-3 during human embryogenesis is much more limited, and mainly restricted to events linked to the first trimester pregnancy. During this period, the expression of galectin-3 is confined to the epithelia, including the skin epithelium, the epithelium lining digestive and respiratory tracts, urothelium and excretory tubes of the kidney. This lectin can also been found in myocardial cells and in the liver, as well as in the peripheral and pre-ossifying chondrocytes and the notochord (Van den Brule et al., 1997). Interestingly, Devouassoux-Shisheboran and colleagues (Devouassoux-Shisheboran et al., 2006) screened normal fetal testes from different ages (8, 20, 25, 30 and 31 weeks of amenorrhea) and found no considerable immunostaining using a specific anti-galectin-3 antibody.

Human adulthood

Human non-haematopoietic tissues

In adult healthy tissues, galectin-3 distribution is ubiquitous but resembles that found during embryogenesis, with a prominent expression in epithelial and myeloid cells. Regarding the gastrointestinal tract, expression of galectin-3 has been described in human gastric epithelial cells, where it can be recognized by O-glycosylated antigens in *Helicobacter pylori*, therefore allowing its adherence to the gastric epithelium (Fowler et al., 2006). Moreover, adhesion of *H. pylori* to gastric cells elicits a rapid release of galectin-3 from infected cells, suggesting that this protein may play a role as a soluble pattern recognition receptor in the host-immune response and may influence the trafficking of phagocytic cells to infectious sites (Fowler et al., 2006). Within the

intestine microenvironment, galectin-3 expression is present along all the segments of the colon, with homogenous distribution in colonic epithelial cells and intestinal macrophages, and decreases at the level of terminal ileum (Lippert et al., 2008). Galectin-3, secreted by colonic epithelial cells, has been proposed to function as a strong activator of colonic lamina propria fibroblasts (Lippert et al., 2008). In addition, its constitutive expression by differentiated enterocytes of normal mucosa may help to prevent inappropriate immune responses against commensal bacteria or food components (Muller et al., 2006). Thus, galectin-glycan lattices may contribute to modulate immune-epithelial cell interactions by influencing immune cell fate and cytokine secretion. Recent evidence indicated that galectin-3 is mainly expressed by crypt epithelial cells and macrophages in the lamina propria of human gut and its specific binding sites are highly represented in intraepithelial gut lymphocytes (Mercer et al., 2009).

Similar to the expression of galectin-3 in mouse liver, no specific staining of hepatocytes was observed in human liver sections processed for immunohistochemical detection. However, intense and reproducible immunostaining was observed in bile duct epithelial cells and DCs consistent with the selective distribution of Kupffer cells (Hsu et al., 1999).

Concerning the expression of galectin-3 in normal lung tissue, Mathieu and colleagues (2005) found robust expression of this protein in bronchial epithelial cells, and strong nuclear staining of chondrocytes of the bronchial cartilage. Moreover, whereas pneumocytes of the alveolar wall showed moderate staining, alveolar macrophages were strongly stained and interstitial fibroblasts presented a staining level comparable to pneumocytes (Mathieu et al., 2005).

The expression of galectin-3 in the human reproductive tract was also investigated by Devouassoux-Shisheboran and colleagues (2006). No specific galectin-3 staining was found in normal testis before puberty. In contrast, a strong and diffuse cytoplasmic staining was detected in Sertoli cells and a weak cytoplasmic positivity was found in few Leydig cells in the post-pubertal normal testicular parenchyma. Within the ovary, no expression was found in granulosa cells, and the surface epithelium was the only tissue component which strongly and diffusely expressed the protein. On the other hand, human endometrial samples and decidual tissue showed abundant expression of galectin-1 and -3, which were tightly controlled throughout the menstrual cycle, consistent with the role of galectin-glycan lattices in regulating inflammatory responses during early pregnancy (von Wolff et al., 2005). Maximal expression of galectin-1 in decidualized stromal cells and of galectin-3 in secretory-phase epithelial glandular cells supports a fundamental role of these glycan-binding proteins in the regulation of endometrial function. Moreover, the established immunomodulatory properties of galectin-3 and its critical function during tumor progression and angiogenesis (Liu and Rabinovich, 2005) are in line with a potential function of this protein in endometrial tissue during implantation.

Although little information is available regarding the expression of galectin-3 in the prostate gland of healthy subjects, immunohistochemical analysis of galectin-3 revealed its prominent expression in benign tissue adjacent to cancer cells and benign intraprostatic areas of prostate cancer patients (Merseburger et al., 2008b). In addition, a decreased expression of galectin-3 was suggested to be involved in the pathogenesis and progression of prostate cancer from benign lesions to hormone-refractory malignant disease (Merseburger et al., 2008b).

In normal human breast, galectin-3 is found in the nucleus and cytoplasm of luminal cells, and also in intralobular fibroblasts (Jones et al., 2004). In human mammary luminal epithelial cells, galectin-3 was found to be associated with ErbB2 expression (Mackay et al., 2003). In addition, down-regulation of this lectin has been implicated in breast cancer progression (Castronovo et al., 1996), and a clear correlation of nuclear galectin-3 expression and poor clinical outcome has been described (Jones et al., 2004).

Low levels of galectin-3 expression were recently detected in kidney glomeruli from healthy individuals, but this expression increased dramatically in the kidneys of nephritic patients suffering systemic lupus erythematosus, suggesting a contribution of this lectin to autoimmune-mediated inflammation (Kang et al., 2009). On the other hand, galectin-3 was found to be uniformly expressed in kidney tubular epithelial cells, and a loss of this protein was implicated in renal carcinogenesis (Merseburger et al., 2008a).

The expression of galectin-3 in normal thyroid tissue remains controversial. Studies aimed at analyzing the expression of this protein in a spectrum of benign and malignant thyroid neoplasms demonstrated that, even though galectin-3 is overexpressed in most papillary carcinomas and some adenomas, normal and benign tissues appear to be negative for this protein (Fernandez et al., 1997; Cvejic et al., 1998). Nevertheless, another study demonstrated the expression of this lectin in epithelial cells of normal thyroid tissue and Hashimoto's thyroiditis (Mehrotra et al., 2004).

Consistent with a prominent expression of galectin-3 in the notochord of human embryos, galectin-3 was detected in the human nucleus pulposus, the notochordal remnant within the intervertebral disc, as well as in chordoma, a tumor derived from notochordal tissue (Gotz et al., 1997). In addition, examination of galectin-3 in adult normal chondrocytes revealed the presence of this endogenous lectin in cytosolic and membrane-enriched fractions of these cells. Of note, this expression was substantially up-regulated in osteoarthritic chondrocytes (Guevremont et al., 2004). In line with these findings, galectin-3, but not galectin-1, was dramatically up-regulated in synovial tissue from patients with juvenile rheumatoid arthritis (Harjacek et

al., 2001). Recent evidence indicated that galectin-3 expression in synovial tissue regulates production of pro-inflammatory cytokines and chemokines by activated fibroblasts (Filer et al., 2009), a critical process during the arthritogenic process.

Galectin-3 is present in coronary artery smooth muscle cells, being required for the adhesion of *Trypanosoma cruzi* to these cardiac cells (Kleshchenko et al., 2004). Finally, in human olfactory epithelium, galectin-3 is limited to cells of the upper one-third portion, in deep contrast to galectin-1 which was found in the basal layer of the epithelium. Considering the potential role of these glycan-binding proteins in cell differentiation and maturation, their differential localization in the olfactory epithelium is consistent with a potential role of these molecules in the physiological turnover of olfactory receptor neurons (Heilmann et al., 2000).

Human haematopoietic tissues

In an attempt to elucidate the role of galectin-3 in immune-inflammatory reactions, Liu and colleagues (1995) found abundant expression of this protein in normal human peripheral blood monocytes and macrophages differentiated *in vitro*. Interestingly, expression of this lectin increased dramatically as human monocytes differentiated into macrophages *in vitro*. Of note, expression of galectin-3 in human monocytes was found to be down-regulated when these cells were exposed to LPS and IFN-γ. These results implied galectin-3 as an autocrine or paracrine regulator of monocyte/macrophage physiology. The functional relevance of this regulated expression is evidenced by the ability of galectin-3 to control superoxide production, phagocytosis and chemotaxis of human monocytes [reviewed in (Yang et al., 2008)].

The transcript profiles of human immature DCs were compared to those of mature DCs (Dietz et al., 2000). Galectin-3 was more abundant in immature than in mature DCs, as shown by transcript levels which were threefold lower in mature compared to immature DCs. This observation appears to diverge from the data recently published by Hsu and colleagues (2009), who observed up-regulation of galectin-3 during maturation of mouse DCs, indicating species-specific differences in galectin-3 expression. Most likely, differences could also be attributed to different maturation stimuli and/or experimental procedures.

Human eosinophils also express galectin-3, which mediates IgE-dependent activation of this cell type (Truong et al., 1993b). Recently, expression of galectin-3 has been demonstrated to favor eosinophil adhesion and rolling under flow, thus supporting the functions of the trafficking of these cells during inflammatory and infectious processes (Rao et al., 2007). Moreover, the expression of galectin-3 was also demonstrated in human neutrophils from normal donors and from patients with inflammatory disorders (Truong et al., 1993a). This lectin has been suggested to induce phosphatydilserine exposure in activated neutrophils without promoting apoptosis (Stowell et al., 2008).

Using light microscopic immunohistochemistry and ultrastructural immunogold labeling, galectin-3 was found to be markedly expressed in human mast cells of several tissues, and in mast cell lines developed *in vitro* from human fetal liver cells (Craig et al., 1995). In the nucleus, immunostaining was detected within the heterochromatin whereas euchromatin was unlabeled. In addition, cytoplasmic labeling was concentrated over secretory granules, suggesting that galectin-3 may be released when these cells are activated to degranulate.

In contrast with its high expression in innate immune cells, galectin-3 is poorly expressed in primary T cells or human T cell lines (Hsu et al., 1996; Fukumori et al., 2003). However, it is abundantly expressed in human T lymphotropic virus (HTLV)-I-infected human T cell lines (Hsu et al., 1996), suggesting induction of this lectin upon viral infection.

D'Haene and colleagues (2005) studied the patterns of immunohistochemical galectin-3 expression in normal human lymphoid tissues, including the tonsils, spleen, thymus and lymph nodes. The authors found that, although most normal lymphoid cells did not express galectin-3, this lectin was detected in follicular DCs and in interdigitating DCs in lymph nodes, and was substantially up-regulated in macrophages and endothelial cells of all lymphoid tissues analyzed. Furthermore, Hassal's corpuscles and thymic epithelial cells also expressed abundant levels of galectin-3. Fewer than 5% of lymphocytes of all tissues analyzed were positive for galectin-3, though no morphological difference was evident between galectin-3-positive and galectin-3-negative lymphocytes.

In a study aimed at understanding the differential susceptibility of thymocyte subsets to galectin-1 and -3, Stillman and colleagues (2006) described the regulated expression of these two lectins in human lymphoid tissues. Galectin-3 was detected throughout the human thymus, in the capsular, cortical, and medullary regions. This lectin was detected surrounding thymocytes and abundantly expressed within thymic epithelial cells in both the cortex and the medulla. The authors confirmed that human thymic epithelial cells not only express, but also externalize both galectin-1 and galectin-3, indicating that developing thymocytes are exposed to both galectins in the thymic microenvironment. Within the lymph node follicle, galectin-1 and -3 were both expressed by follicular DCs. However, in the extrafollicular regions, galectin-3 was expressed in the stroma surrounding small vessels, while galectin-1 was mainly detected in endothelial cells. Thus, T cells in lymph nodes could encounter either galectin-3 or galectin-1, or both galectins, depending on their anatomic compartmentalization. Regarding the function of galectin-3 within the T-cell compartment, recent findings suggested that galectin-3 is an inhibitory regulator of T-cell activation and functions

intracellularly by promoting TCR down-regulation, possibly through the control of the immunological synapse (Chen et al., 2009).

Galectin-3 and cancer

Although most galectins are ubiquitously expressed in various human tissues, these glycan-binding proteins are either silenced or up-regulated in neoplastic tissues. There is an extensive number of published studies reporting a role for galectin-3 in cancer, most of which demonstrate the existence of an altered expression of this lectin in transformed tissues and cancer-associated stroma. This abnormal expression reflects its well-established roles in tumor progression through regulation of carcinogenesis, proliferation, cell migration, angiogenesis and tumor immunity (Califice et al., 2004; Takenaka et al., 2004; van den Brule et al., 2004; Liu and Rabinovich, 2005; Nakahara et al., 2005).

Expression of galectin-3 has recently emerged as a potential diagnostic/prognostic marker of disease progression in some types of cancer [reviewed by (Danguy et al., 2002)]. This lectin has been proposed as a diagnostic marker in renal neoplasms (Dancer et al., 2010) and as a useful tool for differential diagnosis of brain tumors (Park et al., 2008) and small-cell and non-small-cell lung cancer (Buttery et al., 2004). In addition, expression of galectin-3 has been postulated as a novel prognostic marker for breast cancer (Jones et al., 2004). Interestingly, loss of galectin-3 correlates with clear cell renal carcinoma progression (Merseburger et al., 2008a), while decreased galectin-3 expression may be involved in the progression of prostate carcionoma (Merseburger et al., 2008b) and may predict tumor recurrence in bladder cancer (Kramer et al., 2008). However, increased galectin-3 expression may be associated with laryngeal (Miranda et al., 2009), head and neck (Saussez et al., 2007, 2008a) and bladder (Canesin et al., 2010) cancer progression, among others. In addition, high galectin-3 expression has been suggested to be a useful marker for lymph node metastasis in certain types of cancer such as gastric carcinoma (Miyazaki et al., 2002; Dong et al., 2008) and clear cell renal cell carcinoma (Sakaki et al., 2010), while a reduction of galectin-3 expression could be associated with the invasion and metastasis of colorectal cancer (Tsuboi et al., 2007) .

Remarkably, thyroid cancer represents the most studied cancer type regarding the differential expression of galectin-3 and its potential diagnostic and prognostic value. Yet, there is still some controversy; while some authors propose galectin-3 expression as a valuable molecular marker in the diagnosis of thyroid cancer (Faggiano et al., 2002; Cvejic et al., 2003; Pisani et al., 2004; Ersoz et al., 2008), others suggest its lack of significance to distinguish benign from malignant thyroid lesions (Martins et al., 2002; Takano et al., 2003; Mehrotra et al., 2004). In spite of these discrepancies, in a more recent review, Chiu and colleagues (2010) proposed the expression of this endogenous lectin as a very promising diagnostic marker for thyroid cancer.

Interestingly, not only the intensity of galectin-3 expression, but also its subcellular distribution was found to be altered in certain tumor types. Strikingly, nuclear localization of galectin-3 was mainly associated with its anti-tumor effects, whereas its cytoplasmic localization correlated with neoplastic progression (Lotz et al., 1993; Sanjuan et al., 1997; Honjo et al., 2000; van den Brule et al., 2000; Califice et al., 2004; Puglisi et al., 2004).

In addition to the expression of galectin-3 at the tumor site, serum levels of galectin-3 were studied in certain types of cancers, suggesting their diagnostic potential in diffuse large B-cell lymphomas (Kim et al., 2008), bladder carcinoma (Sakaki et al., 2008) and colon carcinoma (Iacovazzi et al., 2010), and their prognostic value to monitor tumor progression and response to therapy in patients with head and neck squamous cell carcinomas (Saussez et al., 2008b). Recently, assessment of serum levels of galectin-3 has also been proposed to have prognostic value in melanoma patients (Vereecken et al., 2009).

The function of galectin-3 in cancer progression is beyond the scope of this article. For detailed information on galectin-3 in cancer, the reader is referred to several compelling reviews (Califice et al., 2004; Takenaka et al., 2004; van den Brule et al., 2004; Liu and Rabinovich, 2005; Nakahara et al., 2005; Nakahara and Raz, 2007).

Concluding Remarks

In recent years galectins have become a major focus of investigation for glycobiologists, cell biologists, immunologists and pathologists. Galectin-3 has emerged as a structurally unique protein expressed in several tissues and cell types with different functions depending on its extracellular or intracellular (nuclear or cytoplasmic) localization. Through protein-saccharide or protein-protein interactions, galectin-3 has been shown to participate in several physiological processes, such as maintenance of cellular homeostasis, immune reactions, organogenesis and angiogenesis, as well as in some pathological processes such as inflammatory disorders, tumor invasion and metastasis. In keeping with its immunomodulatory effects, under physiological conditions galectin-3 shows a prominent expression in highly specialized epithelia, including those covering the digestive tract and lung airways, where it may be involved in mucosal defense systems, controlling immune attack or modulating host-pathogen interactions. On the other hand, an altered expression of galectin-3 in transformed tissues and cancer-associated stroma is usually observed, which reflects the well-established roles of this protein in tumor progression and metastasis by modulating key biological processes, including tumor cell apoptosis, cell cycle progression, cell adhesion,

migration, tumor immunity and angiogenesis. In this regard, the study of galectin-3 as a potential marker with diagnostic or prognostic value represents a promising avenue for future developments. In addition, given its multifunctional properties, this 'chimera-type' lectin has emerged as a therapeutic target, not only in cancer but also in other pathological conditions, including inflammatory disorders, myocardial infarction and atherosclerosis.

Galectin-3 may provide inhibitory or stimulatory signals to control physiological processes, including immune responses, inflammation, neuritogenesis and/or angiogenesis. However, like many other cytokines and growth factors, this lectin may exhibit 'double-edge sword' effects depending on many different factors, including its variable concentrations in distinct tissues, the presence of proteases capable of cleaving essential amino acid residues and modulate its activity, the availability of specific glycan structures on different target cells, its ability to form pentameric or oligomeric structures, and the occurrence of selective post-translational modifications of the molecule (such as phosphorylation) in different tissues. A still unresolved question is how galectin-3 expression is controlled under physiological and pathophysiological conditions. Understanding the multifaceted roles of galectin-3 in basic cellular processes and its regulated expression may contribute to delineate novel therapeutic strategies in autoimmune, inflammatory, allergic and neoplastic processes.

Glossary for the general reader

Akt: thymoma viral proto-oncogene (also referred to as protein kinase B or PKB). Member of the serine/threonine-specific protein kinase family that plays a critical role in controlling survival and apoptosis.

ß-catenin: catenin (cadherin associated protein) beta. Cytoplasmic component of the classical cadherin adhesion complex that forms the adherens junctions in the epithelium and mediates cell-cell adhesion in many other tissues. It is also a key signaling molecule in the canonical Wnt signaling pathway that controls cell growth and differentiation during both normal development and tumorigenesis.

Bcl-2: B-cell leukemia/lymphoma 2. Anti-apoptotic protein, belonging to a family of mammalian gene products, which are involved in the regulation of apoptosis through modulation of mitochondrial outer membrane permeabilization. Bcl-2 family members can be either pro-apoptotic (e.g. Bax, Bad, Bak and Bok) or anti-apoptotic (e.g. Bcl-2, Bcl-xL, and Bcl-w).

CD95: TNF receptor superfamily member 6. Also known as Fas, Fas antigen, apoptosis-mediating surface antigen FAS or APO-1. Cell surface glycoprotein expressed on a broad range of lymphoid cell lines, critically involved in apoptotic cell death.

CRE: Cyclic AMP Response Element. Conserved DNA sequence (5'-TGACGTCA-3') found in some gene promoters, which is recognized by the transcription factor CREB (cAMP responsive element binding protein). Through binding to CRE site in gene promoters, CREB homo- or heterodimers can affect transcription of hundreds of genes.

K-Ras: Ki-ras2 Kirsten rat sarcoma viral oncogene homolog. Encoded by KRAS gene, KRAS protein is a GTPase, found usually tethered to cell membrane, with an essential function in normal tissue signaling. When mutated KRAS is an oncogene, which is involved in the development of many cancers.

Nucling: also known as UACA (uveal autoantigen with coiled-coil domains and ankyrin repeats). Component of the apoptosome complex which participates in the regulation of apoptosis.

PI3K: phosphatidylinositol-3-kinases. Composed of a catalytic and an adaptor subunit, this enzyme participates in signaling pathways that regulate cell growth by phosphorylation of the 3'-OH position of the inositol ring of inositol lipids.

SP1: Specificity Protein 1. Sequence-specific transcription factor involved in gene expression in the early development of an organism. It contains a zinc finger protein motif, by which it binds directly to the consensus sequence 5'-(G/T)GGGCGG(G/A)(G/A)(C/T)-3' at DNA and enhances gene transcription.

Wnt: wingless-related MMTV integration site. Wnt proteins are a family of highly conserved secreted signaling molecules that regulate cell-to-cell interactions during embryogenesis binding to receptors of the Frizzled and LRP (LDL receptor–related protein) families on the cell surface. Specific developmental defects as well as various human diseases, including cancer, are caused by abnormal Wnt signaling.

TCF: T Cell Factors. A family of DNA-binding proteins that are primarily expressed in T-lymphocytes. They interact with ß-catenin and serve as transcriptional activators and repressors in a variety of developmental processes. Also known as LEF (Lymphoid Enhancer Factors).

TCR: T-cell receptor. Heterodimeric glycoprotein receptor composed of either α and ß or γ and δ chains that recognizes foreign antigens and translates such recognition events into intracellular signals that elicit a change in the cell from a dormant to an activated state.

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