Cell. Mol. Life Sci. 63 (2006) 686–697
1420-682X/06/060686-12
DOI 10.1007/s00018-005-5458-8
© Birkhäuser Verlag, Basel, 2006

Cellular and Molecular Life Sciences

Review

Galectin-7

S. Saussez[a] **and R. Kiss**[b, *]

[a] Laboratory of Histology, and Laboratory of Anatomy, Faculty of Medicine and Pharmacy, University of Mons-Hainaut (UMH) (Belgium)
[b] Laboratory of Toxicology – Institute of Pharmacy, Free University of Brussels (ULB), Campus de la Plaine – Boulevard du Triomphe, 1050 Brussels (Belgium), Fax: +322 335 53 35, e-mail: rkiss@ulb.ac.be

Received 30 October 2005; received after revision 15 November 2005; accepted 25 November 2005
Online First 25 January 2006

Abstract. Galectins are a family of animal lectins with an affinity for β-galactosides. They are differentially expressed by various tissues and appear to be functionally multivalent, exerting a wide range of biological activities both during development and in adult tissue. Galectin-7, a member of this family, contributes to different events associated with the differentiation and development of pluristratified epithelia. It is also associated with epithelial cell migration, which plays a crucial role in the re-epithelialization process of corneal or epidermal wounds. In addition, recent evidence indicates that galectin-7, designated as the product of the p53-induced gene 1 (PIG1), is a regulator of apoptosis through JNK activation and mitochondrial cytochrome c release. Defects in apoptosis constitute one of the major hallmarks of human cancers, and galectin-7 can act as either a positive or a negative regulatory factor in tumour development, depending on the histological type of the tumour.

Key words. Galectin-7; epithelium; migration; apoptosis; carcinogenesis.

Introduction

Galectins are animal lectins defined by shared consensus amino acid sequences and an affinity for β-galactose-containing oligosaccharides [1–5]. To date, 15 different galectins have been identified and numbered in order of discovery (galectin-1 to galectin-15) [1–5]. Galectins are widely distributed from lower to higher vertebrates and display a high level of evolutionary preservation. Recent comprehensive reviews detail all these aspects [1–5].

All galectins contain preserved carbohydrate recognition domains (CRDs of approximately 130 amino acids), which are responsible for carbohydrate binding. In terms of their biochemical structure, galectins can be subdivided into three groups, namely those containing one CRD (prototype) and existing as monomers (galectin-5, -7 and -10) or dimers (galectin-1, -2, -11, -13 and -14); those containing two CRDs in tandem connected by a short linker region of up to 70 amino acids (tandem repeat); and galectin-3, which occurs as a chimeric protein with one CRD and an additional non-lectin domain involved in the oligomerization of this protein [1–5]. The present review focuses on galectin-7, with the first section describing the molecular structure of galectin-7 and its ligands.

Galectin-7 was discovered by Madsen and colleagues [6] in their attempt to isolate new markers involved in the maintenance of the normal human epidermal phenotype, and this discovery is discussed in our second section. Galectin-7 expression varies as a function of the levels of differentiation of pluristratified epithelia, and the onset of its expression coincides with the first visible signs of epidermal stratification [7, 8]. Galectin-7 expression therefore seems to be a marker of the differentiation levels of keratinocytes, as outlined in the third section.

Considering the specific roles played by galectin-7 in the context of pluristratified epithelia, it has been shown to have the potential to play a number of crucial roles in ep-

* Corresponding author.

ithelial cell migration and, consequently, in the re-epithelization of corneal and/or epidermal wounds [9–11]. Disorders relating to wound healing constitute a serious medical problem [12, 13]. The roles played by galectin-7 have been investigated on corneal-wound-healing models, and galectin-7 can accelerate re-epithelialization in such types of wounds more efficiently than most known growth factors [14, 15]. These findings have broad therapeutic galectin-7-related implications, as addressed by the fourth section of our review.

The expression of galectin-7 is markedly altered in tumour cells compared to their normal counterparts [7, 16]. In fact, galectin-7 gene expression is induced by the tumour suppressor gene p53 [17], whose major function is to control apoptosis homeostasis [18], and this gene is in fact the one most frequently mutated in human tumours [18]. Galectin-7, which is an apoptosis regulator [19, 20], has been designated as the product of the p53-induced gene 1 (PIG1) [17]. The fifth section of our review is entitled 'Galectin-7 as an apoptosis regulator'.

Defects in apoptosis constitute one of the major hallmarks of human cancers, and galectin-7 can act as either a positive or a negative regulatory factor in tumour development, depending on the histological type of the tumour [21–23]. These features are covered by the final section of our review.

Molecular structure of galectin-7 and its ligands

The X-ray crystal structures of galectin-1 [24], galectin-2 [25], galectin-7 [26], galectin-10 [26] and the CRD domain of galectin-3 [27] have already been described. A considerable wealth of information on the molecular recognition of lectins by carbohydrates has been reported over the past few years on the basis of structural studies [28–31]. In its native form, the X-ray crystal structure of human galectin-7 shows a fold similar to that of prototype galectin-1 and -2, but even more similar to that of galectin-10 [26, 32, 33]. Galectin-7 is like a dimer in the crystalline state [26, 33]. A structure-based sequence alignment of human galectin-7 with known galectin structures reveals a few loop regions adopting significantly different positions such as: (i) the insertion of two residues, Pro10 and Glu11, between strands S1 and F2 (galectin-1, -2 and -10 have similar structures in this region) [26]; (ii) the loop region encompassing residues 39–45 has a conformation different to the corresponding loop in galectin-1 and -2 [26]; (iii) the short loop between residues 55 and 57 has a conformation similar to galectin-2 and differing from galectin-1 and -10 (due to the presence of Cys57) [26]; (iv) the loop containing residues 112–119 closely matches the conformation of the corresponding loop in galectin-10 rather than that of galectin-1 and -2 [26].

The superposition of the carbohydrate-binding sites shows that Arg31 in human galectin-7 occupies the position of His52 in galectin-1 [26]. This arginine residue could form part of the carbohydrate-binding region [26]. Leonidas et al. [26] provided a structural basis for carbohydrate recognition in human galectin-7. At the same time, Seetharaman et al. [27] reported the crystal structure of the human galectin-3 CRD. The overall fold is extremely similar to human galectin-7, and the conformation of the CRD also appears to be retained except in the case of the Arg74 residue (human galectin-7). The molecular weight of galectin-7, determined by ultracentrifugation and sedimentation experiments, strongly suggests that galectin-7 behaves like a dimer in solution, a fact consistent with the presence of a dimer in the crystal structure of the protein [26, 33]. The quaternary structure of this protein is not affected by the binding of LacNac [33].

Galectin-7 can bind to a large panel of potential receptors, as do other galectins. Indeed, galectin-7 binds to non-reducing terminal LacNac residues as well as to internal LacNac oligosaccharide residues [32]. Isothermal titration microcalorimetry and haemagglutination inhibition data demonstrate that, compared to galectin-1 and galectin-3, galectin-7 possesses 6- to 11-fold weaker affinities for carbohydrates with LacNac epitopes [32]. The data we review below indicate that galectin-7 displays opposite effects in terms of tumour progression from one histological type to another. These apparently discrepant data can be explained, at least partly, as follows.

Galectins are found in the cytoplasm, in the nucleus or in the extracellular space. Therefore, there is the possibility that the different functions of galectin-7 may vary according to cellular localization. Such a model has been put forward, for example, to explain the apparent contradictory role of galectin-3 in apoptosis. As we discuss in detail further on, Kuwabara et al. [20] demonstrated that galectin-7 is prone to induce apoptosis in several cell types and that these galectin-7-mediated effects on cell death should be induced in the nucleus rather than in the cytoplasm [20]. Galectin-7 can also bind to cell surface receptors in cell types other than those used by Kuwabara et al. [20] because it can be secreted (see the following section). Intracytoplasmic versus extracytoplasmic roles for galectin-1 and galectin-3 have already been clearly demonstrated. This feature could also be associated with galectin-7 biological functions. As emphasized by Sacchettini and colleagues [34], many biological recognition processes involve the binding and clustering of ligand-receptor complexes and concomitant signal transduction events [34]. Such interactions have been observed in human T cells in which binding and cross-linking of specific glycoprotein counter-receptors on the surface of the cells by an endogenous bivalent carbohydrate-binding protein like galectin-1 leads to apoptosis

[35]. Sacchettini et al. [34] thus report that different counter-receptors associated with specific phosphatase or kinase activities were shown to form separate clusters on the surface of the cells as a result of galectin-1 binding to the carbohydrate moieties of the respective glycoproteins. These authors [34] argue that such data favour the unique separation and organization of signalling molecules that results from galectin-1 binding as being involved in delivering the death signal in T cells. This feature is cell specific and the fact that galectin-7 could behave like galectin-1 remains to be determined. Thus, binding and cross-linking of multivalent carbohydrates with multivalent lectins is shown to be a new paradigm for supermolecular assembly and signal transduction in biological systems [34]. Brewer [36] has recently reviewed the binding and cross-linking properties of galectin-1 and other lectins as a model for the biological signal transduction properties of the galectin family of animal lectins. This model may apply, at least partly, to galectin-7.

The discovery of galectin-7

The skin, which is the largest bodily organ, consists of two layers, i.e. the outer part, which is the epidermis, and the inner part, which is the dermis [37]. The epidermis is firmly attached to the dermis and is constantly regenerated by means of a homeostatic process requiring proliferation, differentiation and apoptosis [37]. A considerable number of research groups have attempted to identify the proteins involved in the maintenance of the normal epidermal phenotype [38–41]. Celis and Olsen [42] have demonstrated that many proteins are regulated differentially in SV40-transformed keratinocytes. One of these proteins corresponds to IEF17 in the keratinocyte database [43, 44], and it seems to be particularly interesting for at least three reasons, i.e. (i) its peptide sequences does not match any known protein [42]; (ii) it is partially secreted by normal keratinocytes into their culture medium [42], and (iii) it is highly down-regulated in SV40-transformed keratinocytes that are anchorage independent and unable to differentiate [42]. Following upon this, Madsen et al. [6] performed the microsequencing and the cDNA cloning of the IEF17 protein and showed that this human protein has a shared identity with the galectin family [45, 46]. IEF17 has been called galectin-7 [6]. IEF17 binds lactose and contains all the amino acids that are central to β-galactoside interaction with the protein [6]. The gene that encodes for galectin-7 maps to chromosome 19 [6]. In fact, the genes coding for galectins are scattered throughout the genome [47, 48]. Galectin-7 is secreted by proliferating, quiescent as well as differentiated keratinocytes into their culture medium [6] despite the fact that its sequence has no typical secretion signal peptide [49]. The absence of a typical secretion signal peptide suggests that galectin-7 is secreted by a non-classical and as yet unknown secretory mechanism. This absence of a typical secretion signal peptide is a common feature of all galectins [50]. A protein called UAT (a urate transporter/channel) has recently been shown to have a high degree of homology with rat, mouse and human galectin-9 and could therefore constitute a galectin-9 isoform [51]. Rappoport et al. [51] have shown that UAT is targeted to plasma membranes in multiple epithelium-derived cell lines and, in polarized cells, to both apical and basolateral membranes. Whereas the amino and carboxy termini of UAT have both been detected on the cytoplasmic side of plasma membranes, cell surface biotinylation studies have demonstrated that UAT is not merely a cytosolic membrane-associated protein but that it also contains at least one extracellular domain. The preliminary data obtained by Rappoport et al. [51] with UAT – a galectin – offer a novel understanding of the potential secretory mechanisms of a galectin-related protein. However, whether the data obtained by Rappoport et al. [51] for UAT can also be applied to other galectin types remains to be determined.

Galectin-7 is found in areas of cell-to-cell contact, and particularly in the upper layers of the human epidermis [6]. Combined with a strong down-regulation of galectin-7 in transformed keratinocytes, this result suggests a role in modulating the cell-cell and cell-matrix interactions necessary for normal growth control. This role is already well known in the case of other members of the galectin family [2, 5, 52, 53].

Galectin-7 as a marker of stratified epithelia

Galectin-7 is mainly found in stratified squamous epithelia [6, 7, 54] as well as in various other types of cancer cells, as detailed below. Considering this epidermal-specific distribution, Magnaldo and colleagues [54] have studied the effect of retinoic acid on galectin-7 expression and distribution in psoriatic epidermis. These authors have shown that in normal adult human skin, galectin-7 is distributed throughout the depth of the epidermis without any apparent difference in intensity in the proliferative (mainly basal) or the differentiated (mainly supra-basal) compartments (fig. 1) [7]. This galectin-7 distribution distinguishes it from the distribution of keratins, a well-known group of epithelial markers, and, particularly, of K5-K14 and involucrin, which are present exclusively in the basal and supra-basal layers [55]. The effect of retinoic acid, a major modulator of the keratinocyte phenotype, on galectin-7 expression differs from that generally observed with standard epidermal markers, which are either induced (basal markers) or repressed (supra-basal markers) by retinoic acids [56]. Indeed, retinoic

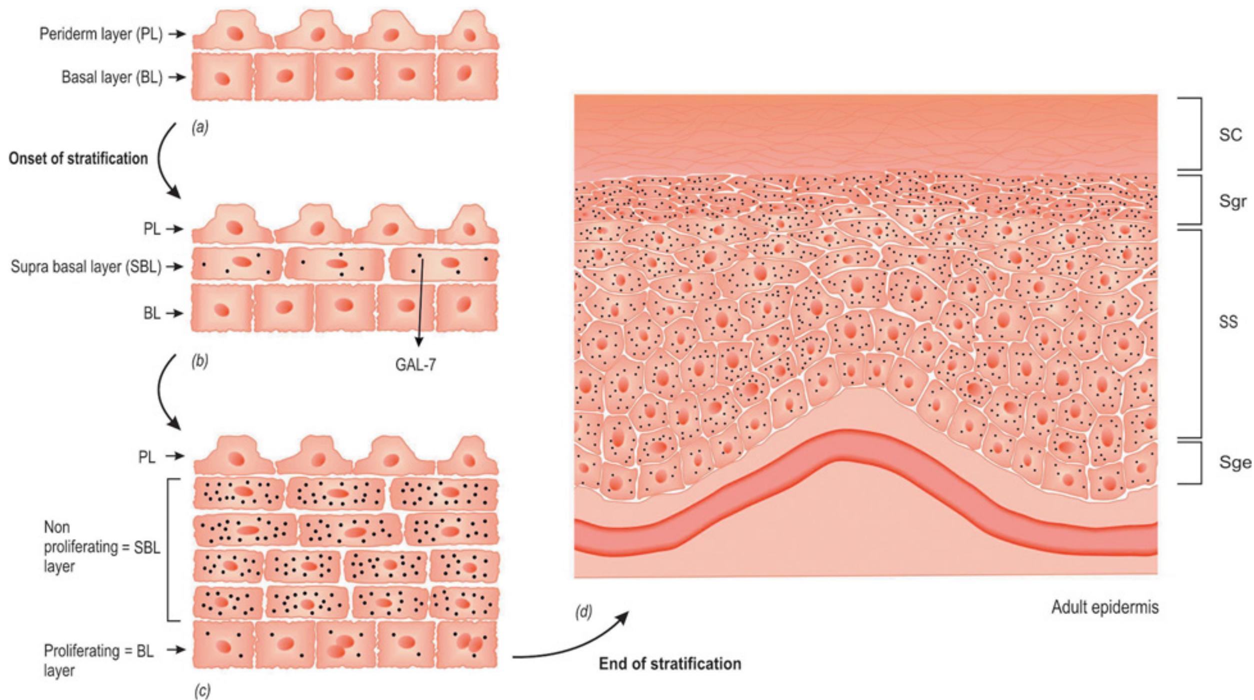

Figure 1: The role of galectin-7 in the stratification of the epidermis. The schemes summarize the arrival and the distribution of galectin-7 during the stratification of the epidermis. Epidermic stratification begins when the supra-basal layer appears between the basal and periderm layers (*A, B*). The onset of galectin-7 expression coincides with the beginning of the process of stratification (*B, C*). Galectin-7 expression is maintained in all living layers; SC, stratum corneum; Sgr, stratum granulosum; SS, stratum spinosum; Sge, stratum germinatum) when the epidermal development is over (*D*).

acid induces an oral metaplasia in cultured epidermal keratinocytes (i.e. a transformation into a non-keratinized stratified epithelium) and reduces the amount of galectin-7, but does not eliminate it [54]. In the psoriatic epidermis, characterized by a parakeratosis attested by the persistence of nuclei and a strong decrease in cornification, the slight reduction in galectin-7 expression in the deepest layers could be linked to the delay in the onset of stratification as observed in this disease [54, 57].

The expression of galectin-7 thus seems to be unique within the epidermis and no other marker displays a similar basal-supra-basal distribution [7, 54]. All the data that we report above therefore suggest that galectin-7 has to be considered as a keratinocyte cell type marker irrespective of the keratinization level and the degree of differentiation within a given epithelium [54]. Magnaldo et al. [7] used *in situ* hybridization and immunolabelling techniques to study the expression of galectin-7 in human, rat and mouse tissue, and observed that galectin-7 is present in interfollicular epidermis, in the outer root sheath of the hair follicle, in the oesophagus and in the oral epithelia, in the cornea and in Hassal's corpuscles of the thymus. Sato and colleagues [58] and Nio et al. [59] have observed similar distributions for galectin-7 in adult mouse tissue by means of Western blot analyses and *in situ* hybridization, respectively. Sato et al. [58] also observed the presence of galectin-7 in the trachea and the ovary, and argued that galectin-7 is produced primarily in stratified epithelia as well as in some wet epithelia, and could therefore play a role in cell-mucus contacts or in the growth of ovarian follicles.

The fact that galectin-7 is present in all stratified epithelia (keratinized or not) therefore suggests that the galectin-7 gene is activated before, or independently of, regional specialization programs. To better circumscribe this hypothesis Timmons et al. [8] studied the expression of galectin-7 during rat and mouse development. Their study revealed the following features (i) No signal is detected during the first half of the gestation period, suggesting that embryonic galectin-7 expression is confined to the second half. (ii) The level of galectin-7 expression clearly correlates with stratification. For example, in the ventral epidermis of mouse embryos, galectin-7 expression is marked in areas where stratification is the most pronounced (i.e. two or more supra-basal cell layers) while it is weak where stratification is less advanced (i.e.

only one supra-basal cell layer) (see fig. 1). The onset of galectin-7 expression coincides with the beginning of stratification. (iv) Galectin-7 is also, and specifically, expressed in the stratified regions of ectodermally derived non-epidermal epithelia such as the lining of the buccal cavity, the oesophagus and the ano-rectal region; no expression is observed in epithelia deriving from the endoderm (the lining of the intestine, the kidneys and the lungs). (v) Galectin-7 expression is maintained in all living layers after epidermal development has been completed.

The study by Timmons et al. [8] thus provides evidence that galectin-7 may be important for both the formation and the maintenance of all stratified epithelia, probably because it modulates cell proliferation and cell interactions irrespective of keratinization or regional specialization.

Figure 1 illustrates the roles of galectin-7 in the processes of epidermal stratification.

Galectin-7 in corneal wound healing

Disorders of corneal or epidermal wound healing, two very similar healing processes, are characterized by impaired or delayed re-epithelialization features and constitute a serious medical problem [13, 14]. Indeed, persistent epithelial defects are characteristic of chronic wounds in elderly decubitus ulcers and venous statis ulcers of the skin, conditions that affect millions of individuals worldwide [13, 14]. Most frequently, re-epithelialization failure is not due to inadequate cell proliferation but to the reduced potential of the epithelium to migrate across the wound bed [60, 61].

Using the cornea as a model, Cao et al. [9–11] were the first to demonstrate the importance of galectin-3 and -7 in the re-epithelialization of wounds. The importance of galectin-3 was highlighted by the fact that the re-epithelialization of corneal wounds was significantly slower in galectin-3-deficient ($gal3^{-/-}$) mice compared with wild-type ($gal3^{+/+}$) mice [10]. Secondly, the exogenous recombinant galectin-3 stimulates the re-epithelialization of corneal wounds in $gal3^{+/+}$ mice in a concentration-dependent manner while it does not accelerate the corneal epithelial wound closure rate in $gal3^{-/-}$ mice [10].

Figure 2 details the roles played by galectin-3 and -7 in corneal wound healing.

In an attempt to understand why re-epithelialization was disturbed in the $gal3^{-/-}$ mice, Cao et al. [9] made use of a cDNA microarray approach to characterize the gene expression patterns of healing $gal3^{+/+}$ and $gal3^{-/-}$ corneas. This gene expression analysis revealed that the healing corneas of the $gal3^{-/-}$ mice contained 12 times fewer galectin-7 gene transcripts than the healing corneas of the wild-type mice. The authors came to the conclusion that galectin-3 may influence the re-epithelialization of wounds, at least in part by modulating the levels of galectin-7 expression [9]. Indeed, galectin-7 accelerated the re-epithelialization of the corneal wounds in the $gal3^{-/-}$ corneas and in the wild-type gal-$3^{+/+}$ mice in a lactose-inhibitable manner [9]. Moreover, the expression of galectin-7 was markedly up-regulated in the corneal epithelium after injury [9, 11]. The glycoconjugates of the corneal epithelial cell surface and the extracellular matrix (ECM) that serve as binding sites for galectin-7 have not yet been characterized. However, Saika et al. [62] have shown that lumican, an unsulphated form of the keratan sulphate proteoglycan, is transiently expressed in the epithelium of healing corneas, and that the epithelial corneal wound closure rate is significantly reduced in lumican-deficient mice. Thus, galectin-7 could bind to lumican, a hypothesis that has to be validated experimentally.

Regardless of the mechanism involved, the findings that galectin-3 and -7 stimulate the re-epithelialization of corneal wounds have broad implications for the development of novel therapeutic strategies for the treatment of non-healing wounds. Indeed, the extent of the acceleration of the re-epithelialization of corneal wounds with galectin-3 and -7 was greater than that reported in most of the published studies using growth factors [12–14]. The clinical potential of galectin-3 and galectin-7 seems to be more attractive than that of growth factors because they have not been shown to induce cell mitosis in epithelial cells [10, 11].

Galectin-7 as an apoptosis regulator

One of the major biological roles played by galectins relates to their modulatory effects on apoptosis; while galectin-3 seems to display an anti-apoptotic activity with various tumour cell lines, several other galectins, including galectin-1, galectin-2, galectin-7 and galectin-9 tend to display pro-apoptotic effects [5, 23, 63–66]. With respect to the anti-apoptotic roles played by galectin-3, the Liu group showed almost a decade ago that galectin-3 inhibits T cell apoptosis induced by the anti-Fas antibody [67]. The Raz group showed that introducing galectin-3 into epithelial cells made them resistant to apoptosis insults [68–70]. In fact, Ser6 phosphorylation acts as a molecular switch for galectin-3 cell translocation from the nucleus to the cytoplasm and, as a result, regulates the anti-apoptotic activity of galectin-3 [71]. And a decade has also passed since the Baum group showed that galectin-1 mediates apoptosis in T cells [72] and in thymocytes [73]. Galectin-1 has a pro-apoptotic effect against T cells by binding to various cell surface receptors including, for example, CD7 [74] and CD45 [75]. Both the Baum and the Rabinovich groups partly analysed at

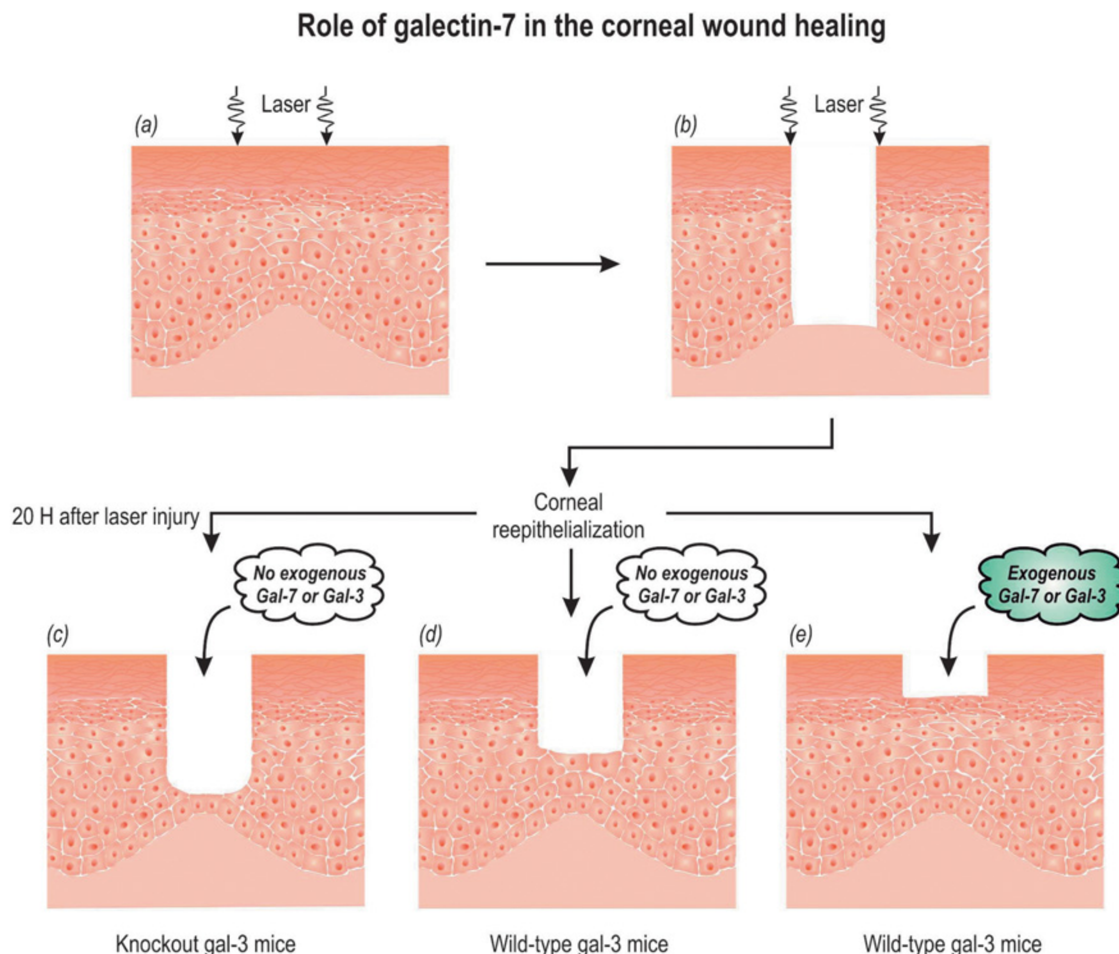

Figure 2. The role of galectin-7 in corneal wound healing. The scheme demonstrates the importance of galectin-3 and -7 in the re-epithelialization of corneal wounds. A transepithelial excimer laser ablation was carried out to produce the corneal wounds (*A, B*). Twenty hours after the laser injury, corneal re-epithelialization was assessed under different conditions, namely in knockout gal-3 mice (*C*), in wild-type gal-3 mice (*D*) and in wild-type gal-3 mice with the exogenous addition of galectin-3 and -7 (*E*). This experimental procedure clearly demonstrates that galectin-3 and -7 stimulate the re-epithelialization of corneal wounds regardless of the mechanism involved. The present figure has been adapted from the work published by Cao et al. [10].

the molecular level the mechanisms by which galectin-1 induces apoptosis in T cells. By way of an example, these mechanisms involve the activation of the AP-1 transcription factor and the down-regulation of Bcl-2 [76], the activation of Lck, Fyn, MEK1/ERK, p38 MAP and the p70S6 kinases [77], mitochondrial hyperpolarization, budding and fission [78] and caspase-independent pathways [79]. The ECM is also involved in galectin-1-mediated T cell death [63]. In addition, galectin-1 can induce T cell death via non-apoptotic mechanisms [80]. Rabinovich's group recently showed that galectin-1 signalling in activated T cells in fact constitutes an important tumour immune escape mechanism, and blocking this inhibitory signal can both allow and potentiate effective immune responses against tumour cells [81]. Indeed, these authors demonstrated that blocking immunosuppressive galectin-1 *in vivo* promotes the rejection of experimental melanomas and stimulates the generation of a tumour-specific T-cell-mediated response in syngeneic mice [81]. Galectin-2 also induces apoptosis in T cells, but differently from galectin-1 [65]. Galectin-9 induces apoptosis in melanoma cells [82].

Galectin-7 also displays pro-apoptotic activity in various types of cell. In fact, on the basis of work with p53-dependent apoptosis onset in DLD-1 colon cancer cell, galectin-7 has been shown to be one of the 14 genes whose expression is induced in the early steps of p53-mediated apoptosis, out of a set of 7002 genes that were analysed [17]. Because UVB radiation is an efficient modulator of gene expression, including p53, and induces apoptosis in epidermal keratinocytes, Bernerd et al. [19] characterized the levels of galectin-7 expression in UVB-induced sunburn/apoptotic keratinocytes, which demonstrated clearly a higher level of galectin-7

expression after exposure. The observations made by Bernerd et al. [19] thus suggest that galectin-7 expression is associated with UVB-induced apoptosis in the epidermis. Galectin-7 expression can be increased after UVB irradiation of the surface of human carcinoma cell lines [83]. Galectin-7 expression is not induced after UVB irradiation in human keratinocyte cell lines lacking wild-type p53 [19]. Taken together, all these data suggest that the UV-induced galectin-7 overexpression in sunburn/apoptotic keratinocytes occurs in cells that have a wild-type p53 function and are endowed with a proliferation potential, because epidermal cells may undergo squamous differentiation independently of p53 integrity [84].

Kuwabara et al. [20] have shown that the ectopic expression of galectin-7 in HeLa and human DLD-1 colon cancer cells renders them more sensitive to apoptosis than wild-type HeLa or DLD-1 cells under various conditions including UV radiation and treatment with either actinomycin D, etoposide, camptothecin or a combination of tumour necrosis factor (TNF)-α and cycloheximide. Further analyses of actinomycin-D-induced apoptosis have demonstrated that galectin-7 expression causes enhanced caspase-3 activity and poly(ADP-ribose) polymerase cleavage, and the potentiation of apoptosis by galectin-7 is completely abrogated by a caspase inhibitor [20]. Kuwabara et al. [20] also observed that galectin-7 transfectants display an accelerated mitochondrial cytochrome c release and an up-regulated JNK activity upon apoptosis induction. These authors report that several lines of evidence indicate that the effect on apoptosis is not due to the lectin functioning extracellularly through interactions with cell surface glycoconjugates, as is the case of galectin-1 with respect to T cells, because galectin-7 is found in the nuclei and cytoplasm of the above-mentioned transfectants [20]. They argue in favour of galectin-7 being a pro-apoptotic protein that functions intracellularly upstream of JNK activation and cytochrome c release [20]. In the same report, Kuwabara et al. [20] referred to the use of DNA microarray analyses that revealed genes differentially expressed between galectin-7 and control transfectants; of these genes, some, such as the redox-related genes monoamine oxidase B, ryanodine receptor 2 and glutathione transferase Mu 3, potentially contribute to the galectin-7 pro-apoptotic function. The murine glutathione *S*-transferase Mu 1–1 gene product regulates apoptosis by binding to ASK1, which activates the JNK pathway [85].

As recently emphasized by Liu and Rabinovich [5], whereas some galectins induce apoptosis by binding to cell surface glycoproteins, others regulate apoptosis through interactions with relevant intracellular proteins. In fact, some pathways by which galectins modulate apoptosis could be common to most, if not all galectins, while more subtle pathways could be specific to certain sub-groups of galectins, or even to individual galectins.

Galectin-7 as a dual regulator of tumour progression, with potential effects on cancer cell migration

Galectins play a number of important roles in cancer development [reviewed in refs. 2, 5, 86]. The altered expression of galectins may contribute to neoplastic transformation and tumour progression through the regulation of cell growth, the cell cycle, angiogenesis, apoptosis and cell migration [2, 5, 86]. As with many galectins, galectin-7 stimulates the growth and/or development of certain tumour types while acting negatively in the development of other tumour types.

At first glance, galectin-7 should aid in the elimination of tumour cells because its expression is induced by p53 and it functions as a regulator of differentiation and apoptosis, as detailed above. However, galectin-7 can also regulate tumour growth negatively, without inducing apoptosis. For example, Ueda et al. [23] found that galectin-7-transfected DLD-1 cells grow significantly more slowly than control transfectants under normal culture conditions in the absence of apoptosis, as that under anchorage-independent cell growth conditions, a significantly lower number of colonies was formed by galectin-7-transfected cells as compared to the control. These authors also observed *in vivo* that galectin-7-transfected DLD-1 cells are associated with lower tumorigenicity than control cells in severe combined immunodeficient mice. The suppressive effect of galectin-7 on DLD-1 colon cancer growth, greater *in vivo* than *in vitro*, may relate to the fact that the ectopic expression of galectin-7 suppresses neoangiogenesis in DLD-1 xenografts [23]. In addition, Kopitz et al. [22] have shown that galectin-7 is a negative growth regulator for human neuroblastoma cells. They demonstrated by means of solid-phase assays that the sugar chain of ganglioside GM1 is a ligand for galectin-7; the GM1 expression increases on the surface of SK-N-MC neuroblastoma cells as a result of up-regulated ganglioside sialidase activity, a key factor for the switch from proliferation to differentiation in these neuroblastoma cells [22]. In serum-supplemented proliferation assays, galectin-7 reduces neuroblastoma cell growth without the appearance of any of the features characteristic of classical apoptosis [22]. Thus, galectin-7 can play a negative role in tumour development by regulating apoptosis-related as well as non-apoptotic features in tumour growth.

In sharp contrast to the intuitively negative roles played by galectin-7 in tumour development, Demers et al. [87] recently reported a study in which they uncovered the existence of a previously undescribed activity of galectin-7,

namely the promotion of cancer cell malignancy. Indeed, Demers et al. [87] found that the development of experimental thymic lymphoma is accelerated when induced by lymphoma cells overexpressing galectin-7. These authors provide data suggesting that galectin-7 modulates the aggressive behaviour of lymphoma cells by controlling the expression of metastatic genes, such as the metalloproteinase MMP-9 [87]. The results reported by Demers et al. [87] concerning the positive effect of galectin-7 on tumour development are also supported by the data reported by Lu et al. [88] and Moisan et al. [21]. Lu et al. [88] show that galectin-7 is overexpressed in rat mammary carcinomas induced by 7,12-dimethylbenz[a]anthracene. Thus, an overexpression of galectin-7 stands in direct relation to the increased biological aggressiveness in experimental tumours. To ascertain the complex pattern of gene expression involved in the evolution of aggressiveness in lymphoma cells, Moisan et al. [21] compared the transcriptome of 164T2 lymphoma cells with that of their aggressive variants. These authors thus identified several genes that are differentially expressed in non-metastatic lymphoma cells and their metastatic variants [21]. Galectin-7 is one of the gene products whose expression is significantly up-regulated in the metastatic variant. The explanation given by Moisan et al. [21] for the involvement of galectin-7 in the metastatic processes of lymphoma cells relates mainly to the methylation of the galectin-7 gene. DNA methylation of a number of genes had previously been associated with the transformation of normal cells into tumour cells or the progression from a non-metastatic phenotype to a metastatic one [89, 90]. In some instances, the DNA methylation of a single CpG dinucleotide is sufficient to control the expression of p53 [91]. While the galectin-7 tissue distribution is very narrow (mostly present in all stratified epithelia), an examination of the human galectin-7 promoter reveals a strong transcriptional potential conferred by the presence of three repeats of the GGGTGG motif present in the 5′-flanking sequence [21, 88]. The specificity of the tissue expression of galectin-7 suggests that its expression is controlled by strong suppressive factors, a feature in which DNA methylation may play a major role. Indeed, the data provided by Moisan et al. [21] show that the treatment of lymphoma cells with 5-aza-CdR, an agent which modulates the levels of DNA methylation, contributes to the up-regulation of galectin-7. In reference to a work published by Kuwabara et al. [20], who show that stable transfectants of Hela cells expressing galectin-7 exhibit an enhanced sensitivity to apoptosis while expressing a large set of other genes, Moisan et al. [21] hypothesized that while highly metastatic variants of lymphoma cells overexpressing galectin-7 have evolved towards a state of resistance to the pro-apoptotic function of galectin-7, their aggressiveness has emerged from the galectin-7 function itself and/or from genes induced by its presence. We have also observed that galectin-7 expression is markedly down-regulated in benign thyroid tumours compared to malignant ones [92].

As reviewed in the previous section and also recently emphasized by Liu and Rabinovich [5], the most extensively studied function of galectins that is relevant to tumour progression is the regulation of apoptosis. However, another major role played by galectins with respect to tumour progression relates to their direct or indirect involvement in cancer cell migration leading to the formation of metastases.

While cell migration is an adaptive process subject to cell-type- and environment-specific modifications, the principle events involved in cell migration in ECM environments can be schematically broken down into a number of interdependent steps [93, 94]. The first of these consists of initial cell polarization driven by actin polymerization into filaments, which is followed by the extension of cytoplasmic protrusions or pseudopods. The second step results from the contact with the ECM ligands of the adhesion receptors (most notably those belonging to the integrin and galectin families) located on the surface of the protrusion [5, 95–98]. These interaction zones recruit cytoplasmic adaptor, signalling and cytoskeletal proteins towards the adhesion site to form focal adhesions or focal contacts [99, 100]. The third step involves matrix-degrading proteases such as MMPs and serine proteases, which are needed for local proteolysis of adjacent ECM proteins, this proteolysis enabling in turn the forward expansion of the cell body [101, 102]. After (or during) integrin-ligand binding, the fourth step consists of interactions between the actin filaments and cross-linking and contractile proteins (such as myosin II), which stabilize and contract the actin strands. The fifth step consists of local cell contractions based on the shortening of membrane-anchored actin filaments, resulting in the forward movement of the rear part of the cell and its translocation along the substrate. The actin dynamics, of which heavy use is made during cell migration (e.g. for cell polarization, protrusion extensions and cell elongation and contraction) are under the control of members of the small Rho GTPase family and their effectors [103, 104].

Our group has already demonstrated the major roles played by various galectins in tumour cell migration. These include galectin-1 in gliomas [105] and in eosinophils [106], and galectin-1, -3 [107] and -8 [108] in colon cancer. We have also shown that modulating the levels of expression of galectin-1 in human glioma cells markedly modifies the organization of the actin cytoskeleton in relation to modifications in RhoA GTPase expression [105, 109]. Hikita et al. [110] have demonstrated that the secretion of galectin-3 by epithelial cells is required for the correct polymerization of ECM components such as hensin, a glycoprotein responsible for the polarization of intercalated columnar epithelial cells.

The galectin-mediated modulation of cancer cell migration may, at least in part, relate to the fact that galectins cooperate closely with integrins in cell-cell and cell-ECM interactions. Indeed, using cross-linking experiments, dimeric galectin-1 was found to bind to and retain the β1 cell surface integrin [111] and to modulate the adhesion of melanoma cells on laminin [112]. Galectin-8 has been reported as promoting cell adhesion and migration upon binding to a subset of β1 integrins and to trigger cytoskeleton re-organization, including the formation of F-actin-containing microspikes [113, 114]. Knocking down galectin-3 expression in glioma cells results in an overexpression of the α6 integrin in association with an increased glioma cell motility on a laminin substrate [115]. In human breast carcinoma cells, galectin-3 overexpression is associated with an increased cell surface expression of the $\alpha6\beta1$ integrin (leading to an enhanced adhesion to extracellular matrix proteins), with an increase in invasiveness [116], and with an increase in the levels of $\alpha7\beta1$ integrin expression, a process which is linked to protection from apoptosis [117]. In Hela cells stably transfected with galectin-7, a four-fold increase in α1 integrin mRNA has been observed [20]. Thus, the possibility remains that galectin-7 could modulate cancer cell migration by interacting with specific integrins. Chen et al. [16] have already demonstrated by means of proteomic analyses that galectin-7 is overexpressed in buccal squamous cell carcinomas compared to normal buccal epithelia. Cao et al. [11] have reported a number of potential roles for galectin-7 as a mediator of corneal epithelial cell migration. Galectin-7 can therefore be suspected of displaying a number of important roles in cancer cell migration, at least in those cancers arising from pluristratified epithelia, including, for example, some types of head and neck squamous cell carcinomas, a topic on which we are currently working.

Pharmacological weapons have been developed against galectin-7 including, for example, the use of phenyl thio-beta-D-galactopyranosides [118]. Since the direct implication of galectin-7 has been clearly demonstrated in several tumour systems, it would be interesting to test such compounds on tumour systems where the direct involvement of galectin-7 is strongly suspected. Such studies could determine whether galectin-7 is involved in cancer cell migration in the case of tumour types on whose development galectin-7 is already known to have significant effects.

1 Rabinovich G. A. (1999) Galectins: an evolutionarily conserved family of animal lectins with multifunctional properties: a trip from the gene to clinical therapy. Cell Death. Differ. **6:** 711–721

2 Danguy A., Camby I. and Kiss R. (2002) Galectins and cancer. Biochim. Biophys. Acta **1572:** 285–293

3 Liu F. T., Patterson R. J. and Wang J. L. (2002) Intracellular functions of galectins. Biochim. Biophys. Acta **1572:** 263–273

4 Leffler H., Carlsson S., Hedlund M., Qian Y. and Poirier F. (2004) Introduction to galectins. Glycoconj. J. **19:** 433–440

5 Liu F. T. and Rabinovich G. (2005) Galectins as modulators of tumour progression. Nat. Rev. Cancer **5:** 29–41

6 Madsen P., Rasmussen H. H., Flint T., Gromov P., Kruse T. A., Honore B. et al. (1995) Cloning, expression, and chromosome mapping of human galectin-7. J. Biol. Chem. **270:** 5823–5829

7 Magnaldo T., Fowlis D. and Darmon M. (1998) Galectin-7, a marker of all types of stratified epithelia. Differentiation **63:** 159–168

8 Timmons P. M., Colnot C., Cail I., Poirier F. and Magnaldo T. (1999) Expression of galectin-7 during epithelial development coincides with the onset of stratification. Int. J. Dev. Biol. **43:** 229–235

9 Cao Z., Wu H. K., Bruce A., Wollenberg K. and Panjwani N. (2002) Detection of differentially expressed genes in healing mouse corneas, using cDNA microarrays. Invest. Ophthalmol. Vis. Sci. **43:** 2897–2904

10 Cao Z., Said N., Amin S., Wu H. K., Bruce A., Garate M. et al. (2002) Galectins-3 and -7, but not galectin-1, play a role in re-epithelialization of wounds. J. Biol. Chem. **277:** 42299–42305

11 Cao Z., Said N., Wu H. K., Kuwabara I., Liu F. T. and Panjwani N. (2003) Galectin-7 as a potential mediator of corneal epithelial cell migration. Arch. Ophthalmol. **121:** 82–86

12 Eaglstein W. H. and Falanga V. (1997) Chronic wounds. Surg. Clin. North Am. **77:** 689–700

13 Singer A. J. and Clark R. A. F. (1999) Cutaneous wound healing. N. Engl. J. Med. **341:** 738–746

14 Schultz G., Khaw P. T., Oxford K., MaCauley S., Van Setten G. and Chegini N. (1994) Growth factors and ocular wound healing. Eye **8:** 184–187

15 Zieske J. D. and Gipson I. K. (2000) Agents that affect corneal wound healing: modulation of structure and function. In: Principles and Practice of Ophthalmology, 2nd edn., pp. 364–372 Albert D. M. and Jakobiec F. A. (eds.) Philadelphia

16 Chen J., He Q. Y., Yuen A. P. and Chiu J. F. (2004) Proteomics of buccal squamous cell carcinoma: the involvement of multiple pathways in tumorigenesis. Proteomics **4:** 2465–2475

17 Polyak K., Xia Y., Zweier J., Kinzler K. and Vogelstein B. (1997) A model for p53-induced apoptosis. Nature **389:** 300–305

18 Sigal A. and Rotter V. (2000) Oncogenic mutations of the p53 tumor suppressor: the demons of the guardian of the genome. Cancer Res. **60:** 6788–6793

19 Bernerd F., Sarasin A. and Magnaldo T. (1999) Galectin-7 overexpression is associated with the apoptotic process in UVB-induced sunburn keratinocytes. Proc. Natl. Acad. Sci. USA. **96:** 11329–11334

20 Kuwabara I., Kuwabara Y., Yang R. Y., Schuler M., Green D. R., Zuraw B. L. et al. (2002) Galectin-7 (PIG1) exhibits pro-apoptotic function through JNK activation and mitochondrial cytochrome c release. J. Biol. Chem. **277:** 3487–3497

21 Moisan S., Demers M., Mercier J., Magnaldo T., Potworowski E. F. and St-Pierre Y. (2003) Upregulation of galectin-7 in murine lymphoma cells is asociated with progression toward an aggressive phenotype. Leukemia **17:** 751–759

22 Kopitz J., André S., Reitzenstein C. von, Versluis K., Kaltner H., Pieters RJ. et al. (2003) Homodimeric galectin-7 (p53-induced gene 1) is a negative growth regulator for human neuroblastoma cells. Oncogene **22:** 6277–6288

23 Ueda S., Kuwabara I. and Liu F. T. (2004) Suppression of tumor growth by galectin-7 gene transfer. Cancer Res. **64:** 5672–5676

24 Bourne Y., Bolgiano B., Liao D., Strekcer G., Cantau P.,,Herzberg O. et al. (1994) Crosslinking of mammalian lectin (galectin-1) by complex biantennary saccharides. Nat. Struct. Biol. **1:** 863–870

25 Lobsanov Y. D., Gitt M. A., Leffler H., Barondes S. H. and Rini J. M. (1993) X-ray crystal structure of the human dimeric

S-Lac lectin, L-14-II, in complex with lactose at 2.9-Å resolution. J. Biol. Chem. **268:** 27034–27038
26 Leonidas D. D., Vatzaki E. H., Vorum H., Celis J. E., Madsen P. and Acharya K. R. (1998) Structural basis for the recognition of carbohydrates by human galectin-7. Biochemistry **37:** 13930–13940
27 Setharaman J., Kanigsberg A., Slaaby R., Leffler H., Barondes S. H. and Rini J. M. (1998) X-ray crystal structure of the human galectin-3 carbohydrate recognition domain at 2.1-Å resolution. J. Biol. Chem. **273:** 13047–13052
28 Rini J. M. (1995) X-ray crystal structures of animal lectins. Curr. Opin. Struct. Biol. **5:** 617–621
29 Weis W. I. and Drickamer K. (1996) Structural basis of lectin-carbohydrate recognition. Annu. Rev. Biochem. **65:** 441–473
30 Gabius H. J. (1997) Concepts of tumor lectinology. Cancer Invest. **15:** 454–464
31 Lis H. and Sharon N. (1998) Lectins: carbohydrate-specific proteins that mediate cellular recognition. Chem. Rev. **98:** 637–674
32 Brewer C. F. (2004) Thermodynamic binding studies of galectin-1, -3 and -7. Glycoconj. J. **19:** 459–465
33 Morris S., Ahmad N., André S., Kaltner H., Gabius H. J., Brenowitz M. et al. (2004) Quaternary solution structures of galectins-1, -3, and -7. Glycobiology **14:** 293–300
34 Sacchettini J. C., Baum L. G. and Brewer C. F. (2001) Multivalent protein-carbohydrate interactions: a new paradigm for supermolecular assembly and signal transduction. Biochemistry **40:** 3009–3015
35 Pace K. E., Lee C., Stewart P. L. and Baum L. G. (1999) Restricted receptor segregation into membrane microdomains occurs on human T cells during apoptosis induced by galectin-1. J. Immunol. **163:** 3801–3811
36 Brewer C. F. (2002) Binding and cross-linking properties of galectins. Biochim. Biophys. Acta **1572:** 255–262
37 Kierszenbaum A. L. (2002) Histology and Cell Biology: An Introduction to Pathology, pp. 299–308, Mosby, St. Louis
38 Bar-Sagi D. and Feramisco J. R. (1985) Microinjection of the ras oncogene protein into PC12 cells induces morphological differentiation. Cell **42:** 841–848
39 Greig R. G., Koestler T. P., Trainer D. L., Corwin S. P., Miles L., Kline T. et al. (1985) Tumorigenic and metastatic properties of 'normal' and ras-transfected NIH/3T3 cells. Proc. Natl. Acad. Sci. USA **82:** 3698–3701
40 Kamps M. P., Buss J. E. and Sefton B. M. (1985) Mutation of NH2-terminal glycine of p60src prevents both myristoylation and morphological transformation. Proc. Natl. Acad. Sci. USA. **82:** 4625–4628
41 Ponta H., Sleeman J. and Herrlich P. (1994) Tumor metastasis formation: cell-surface proteins confer metastasis-promoting or -suppressing properties. Biochim. Biophys. Acta **1198:** 1–10
42 Celis J. E. and Olsen E. (1994) A qualitative and quantitative protein database approach identifies individual and groups of functionally related proteins that are differentially regulated in simian virus 40 (SV40) transformed human keratinocytes: an overview of the functional changes associated with the transformed phenotype. Electrophoresis **15:** 309–344
43 Celis J. E., Rasmussen H. H., Madsen P., Leffers H., Honore B., Dejgaard K. et al. (1992) The human keratinocyte two-dimensional gel protein database (update 1992): towards an integrated approach to the study of cell proliferation, differentiation and skin diseases. Electrophoresis **13:** 893–959
44 Celis J. E., Rasmussen H. H., Olsen E., Madsen P., Leffers H., Honore B. et al. (1993) The human keratinocyte two-dimensional gel protein database: update 1993. Electrophoresis **14:** 1091–1198
45 Barondes S. H., Castronovo V., Cooper D. N., Cummings R. D., Drickamer K., Feizi T. et al. (1994) Galectins: a family of animal beta-galactoside-binding lectins. Cell **76:** 597–598
46 Barondes S. H., Cooper D. N., Gitt M. A. and Leffler H. (1994) Galectins: structure and function of a large family of animal lectins. J. Biol. Chem. **269:** 20807–20810
47 Raz A., Carmi P., Raz T., Hogan V., Mohamed A. and Wolman S. R. (1991) Molecular cloning and chromosomal mapping of a human galactoside-binding protein. Cancer Res. **51:** 2173–2178
48 Mehrabian M., Gitt M. A., Sparkes R. S., Leffler H., Barondes S. H. and Lusis A. J. (1993) Two members of the S-lac lectin gene family, LGALS1 and LGALS2, reside in close proximity on human chromosome 22q12-q13. Genomics **15:** 418–420
49 Kuchler K. (1993) Unusual routes of protein secretion: the easy way out. Trends Cell Biol. **3:** 421–426
50 Nickel W. (2003) The mystery of nonclassical protein secretion: a current view on cargo proteins and potential export routes. Eur. J. Biochem. **270:** 2109–2119
51 Rappoport J. Z., Lipkowitz M. S. and Abramson R. G. (2001) Localization and topology of a urate transporter/channel, a galectin, in epithelium-derived cells. Am. J. Physiol. Cell Physiol. **281:** 1926–1939
52 Liu F. T. (2005) Regulatory roles of galectins in the immune response. Int. Arch. Allergy Immunol. **136:** 385–400
53 Stillman B. N., Mischel P. S. and Baum L. G. (2005) New roles for galectins in brain tumors – from prognostic markers to therapeutic targets. Brain Pathol. **15:** 124–132
54 Magnaldo T., Bernerd F. and Darmon M. (1995) Galectin-7,a human 14-kDa S-lectin, specifically expressed in keratinocytes and sensitive to retinoic acid. Dev. Biol. **168:** 259–271
55 Fuchs E. (1990) Epidermal differentiation: the bare essentials. Curr. Opin. Cell Biol. **2:** 1028–1035
56 Asselineau D., Bernard B. A., Bailly C. and Darmon M. (1989) Retinoic acid improves the morphogenesis of human epidermis *in vitro*. Dev. Biol. **133:** 322–335
57 Bernerd F., Magnaldo T. and Darmon M. (1992) Delayed onset of epidermal differentiation in psoriasis. J. Invest. Dermatol. **98:** 902–910
58 Sato M., Nishi N., Shoji H., Kumagai M., Imaizumi T., Hata Y. et al. (2002) Quantification of galectin-7 and its localization in adult mouse tissues. J. Biochem. (Tokyo) **131:** 255–260
59 Nio J., Kon Y. and Iwanaga T. (2005) Differential cellular expression of galectin family mRNAs in the epithelial cells of the mouse digestive tract. J. Histochem. Cytochem. **53:** 1323–1334
60 Seiler W. O., Stähelin H. B., Zolliker R., Kallenberg A. and Luscher N. J. (1989) Impaired migration of epidermal cells from decubitus ulcers in cell cultures: a cause of protracted wound healing? Am. J. Clin. Pathol. **92:** 430–434
61 Woodley D. Re-epithelization. (1996) In: The Molecular and Cellular Biology Of Wound Repair 2nd edn., pp. 339–354, Clark R. A. F. (ed.), Plenum, New York
62 Saika S., Shiralshi A., Liu C. Y., Funderburgh J. L., Kao C. W. and Kao W. W. (2000) Role of lumican in the corneal epithelium during wound healing. J. Biol. Chem. **275:** 2607–2612
63 He J. and Baum L. G. (2004) Presentation of galectin-1 by extracellular matrix triggers T cell death. J. Biol. Chem. **279:** 4705–4712
64 Hoyer K. K., Pang M., Gui D., Shintaku I. P., Kuwabara I., Liu F. T. et al. (2004) An anti-apoptotic role for galectin-3 in diffuse large B-cell lymphomas. Am. J. Pathol. **164:** 893–902
65 Sturm A., Lensch M., André S., Kaltner H., Wiedenmann B., Rosewicz S. et al. (2004) Human galectin-2: novel inducer of T cell apoptosis with distinct profile of caspase activation. J. Immunol. **173:** 3825–3837
66 Nakahara S., Oka N. and Raz A. (2005) On the role of galectin-3 in cancer apoptosis. Apoptosis **10:** 267–275
67 Yang R. Y., Hsu D. K. and Liu F. T. (1996) Expression of galectin-3 modulates T-cell growth and apoptosis. Proc. Natl. Acad. Sci. USA **93:** 6737–6742

68 Akahani S., Makker P. N., Inohara H., Kim H. R. and Raz A. (1997) Galectin-3: a novel antiapoptotic molecule with a functional BH1 (NWGR) domain of Bcl-2 family. Cancer Res. **57:** 5272–5276
69 Kim H. R., Lin H. M., Biliran H. and Raz A. (1999) Cell cycle arrest and inhibition of anoikis by galectin-3 in human breast epithelial cells. Cancer Res. **59:** 4148–4154
70 Yoshii T., Fukumori T., Honjo Y., Inohara H., Kim H. R. C. and Raz A. (2002) Galectin-3 phosphorylation is required for its anti-apoptotic function and cell cycle arrest. J. Biol. Chem. **277:** 6852–6857
71 Takenaka Y., Fukumori T., Yoshii T., Oka N., Inohara H., Kim H. R. C. et al. (2004) Nuclear export of phosphorylated galectin-3 regulates its antiapoptotic activity in response to chemotherapeutic drugs. Mol. Cell. Biol. **24:** 4395–4406
72 Perillo N. L., Pace K. E., Seilhamer J. J. and Baum L. G. (1995) Apoptosis of T cells mediated by galectin-1. Nature **378:** 736–739
73 Perillo N. L., Uittenbogaart C. H., Nguyen J. T. and Baum L. G. (1997) Galectin-1, an endogeneous lectin produced by thymic epithelial cells, induces apoptosis of human thymocytes. J. Exp. Med. **185:** 1851–1858
74 Roberts A. A., Amano M., Felten C., Galvan M., Sulur G., Pinter-Brown L. et al. (2003) Galectin-1-mediated apoptosis in mycosis fungoides: the roles of CD7 and cell surface glycosylation. Mod. Pathol. **16:** 543–551
75 Nguyen J. T., Evans D. P., Galvan M., Pace K. E., Leitenberg D., Bui T. N. et al. (2001) CD45 modulates galectin-1-induced T cell death: regulation by expression of core 2 O-glycans. J. Immunol. **167:** 5697–5707
76 Rabinovich G. A., Alonso C. R., Sotomayor C. E., Durand S., Bocco J. L. and Riera C. M. (2000) Molecular mechanisms implicated in galectin-1-induced apoptosis: activation of the AP-1 transcription factor and downregulation of Bcl-2. Cell Death Differ. **7:** 747–753
77 Fuertes M. B., Molinero L. L., Toscano M. A., Ilarregui J. M., Rubinstein N., Fainboim L. et al. (2004) Regulated expression of galectin-1 during T-cell activation involves Lck and Fyn kinases and signalling through MEK1/ERK, p38 MAP kinase and p70S6 kinase. Mol. Cell Biochem. **267:** 177–185
78 Matarrese P., Tinari A., Mormone E., Bianco G. A., Toscano M. A., Ascione B. et al. (2005) Galectin-1 sensitizes resting human T lymphocytes to Fas (CD95)-mediated cell death via mitochondrial hyperpolarization, budding and fission. J. Biol. Chem. **280:** 6969–6985
79 Hahn H. P., Pang M., He J., Hernandez J. D., Yang R. Y., Li L. Y. et al. (2004). Galectin-1 induces nuclear translocation of endonuclease G in caspase- and cytochrome c-independent T cell death. Cell Death Differ. **11:** 1277–1286
80 Rabinovich G. A., Ramhorst R. E., Rubinstein N., Corigliano A., Daroqui M. C., Kier-Joffe E. B. et al. (2002) Induction of allogenic T-cell hyporesponsiveness by galectin-1-mediated apoptotic and non-apoptotic mechanisms. Cell Death Differ. **9:** 661–670
81 Rubinstein N., Alvarez M., Zwirner N. W., Toscano M. A., Ilarregui J. M., Bravo A. et al. (2004) Targeted inhibition of galectin-1 gene expression in tumor cells results in heightened T cell-mediated rejection: a potential mechanism of tumor-immune privilege. Cancer Cell **5:** 241–251
82 Kageshita T., Kashio Y., Yamauchi A., Seki M., Abedin M. J., Nishi N. et al. (2002) Possible role of galectin-9 in cell aggregation and apoptosis of human melanoma cell lines and its clinical significance. Int. J. Cancer **99:** 809–816
83 Condaminet B., Redziniac G., Monsigny M. and Kieda C. (1997) Ultraviolet rays induced expression of lectins on the surface of a squamous carcinoma keratinocyte cell line. Exp. Cell Res. **232:** 216–224
84 Donehower L. A., Harvey M., Slagle B. L., McArthur M. J., Montgomery C. A. Jr, Butel J. S. et al. (1992) Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. Nature **356:** 215–221
85 Cho S. G., Lee Y. H., Park H. S., Ryoo K., Kang K. W., Park J. et al. (2001) Glutathione S-transferase mu modulates the stress-activated signals by suppressing apoptosis signal-regulating kinase 1. J. Biol. Chem. **276:** 12749–12755
86 Califice S., Castronovo V. and Van Den Brule F. (2004) Galectin-3 and cancer. Int. J. Oncol. **25:** 983–992
87 Demers M., Magnaldo T. and St-Pierre Y. (2005) A novel function for galectin-7: promoting tumorigenesis by up-regulating MMP-9 gene expression. Cancer Res. **65:** 5205–5210
88 Lu J., Pei H., Kaeck M. and Thompson H. J. (1997) Gene expression changes associated with chemically induced rat mammary carcinogenesis. Mol. Carcinog. **20:** 204–215
89 Laird P. W. and Jaenisch R. (1996) The role of DNA methylation in cancer genetic and epigenetics. Annu. Rev. Genet. **30:** 441–464
90 Baylin S. B. and Herman J. G. (2000) DNA hypermethylation in tumorigenesis: epigenetics joins genetics. Trends Genet. **16:** 168–174
91 Pogribny I. P., Pogribna M., Christman J. K. and James S. J. (2000) Single-site methylation within the p53 promoter region reduces gene expression in a reporter gene construct: possible *in vivo* relevance during tumorigenesis. Cancer Res. **60:** 588–594
92 Rorive S., Eddafali B., Fernandez S., Decaestecker C., André S., Kaltner H. et al. (2002) Changes in galectin-7 and cytokeratin-19 expression during the progression of malignancy in thyroid tumors: diagnostic and biological implications. Mod. Pathol. **15:** 1294–1301
93 Lauffenburger D. A. and Horwitz A. F. (1996) Cell migration: a physically integrated molecular process. Cell **84:** 359–369
94 Friedl P. and Wolf K. (2003) Cell-cell invasion and migration: diversity and escape mechanisms. Nat. Rev. Cancer **3:** 362–374
95 Giancotti F. G. and Ruoslahti E. (1999) Integrin signalling. Science **285:** 1028–1032
96 Hood J. D. and Cheresh D. A. (2002) Role of integrins in cell invasion and migration. Nat. Rev. Cancer **2:** 91–100
97 Lefranc F., Brotchi J. and Kiss R. (2005a) Possible future issues in the treatment of glioblastomas, with a special emphasis on cell migration and the resistance of migrating glioblastoma cells to apoptosis. J. Clin. Oncol. **23:** 2411–2422
98 Lefranc F., Mijatovic T., Decaestecker C., Kaltner H., André S., Brotchi J. et al. (2005b) Monitoring the expression profiles of integrins and adhesion/growth regulatory galectins in adamantinomatous craniopharyngiomas: their ability to regulate tumor adhesiveness to surrounding tissue and their contribution to prognosis. Neurosurgery **56:** 763–776
99 Martin K. H., Slack J. K., Boerner S. A., Martin C. C. and Parsons J. T. (2002) Integrin connections map: to infinity and beyond. Science **296:** 1652–1653
100 Galbraith C. G., Yamada K. M. and Sheetz M. P. (2002) The relationship between force and focal complex development. J. Cell Biol. **159:** 695–705
101 Brinckerhoff C. E. and Matrisian L. M. (2002) Matrix metalloproteinases: a tail of a frog that became a prince. Nat. Rev. Mol. Cell Biol. **3:** 207–214
102 Mott J. D. and Werb Z. (2004) Regulation of matrix biology by matrix metallopro-teinases. Curr. Opin. Cell Biol. **16:** 558–564
103 Etienne-Manneville S. and Hall A. (2002) Rho GTPases in cell biology. Nature **420:** 629–635
104 Ridley A. J. (2001) Rho GTPases and cell migration. J. Cell Sci. **114:** 2713–2722
105 Camby I., Belot N., Lefranc F., Sadeghi N., Launoit Y. de, Kaltner H. et al. (2002) Galectin-1 modulates human glioblastoma cell migration into the brain through modifications to the actin cytoskeleton and the levels of expression of small GTPases. J. Neuropathol. Exp. Neurol. **61:** 585–597

106 Delbrouck C., Doyen I., Belot N., Decaestecker C., Ghanooni R., Lavareille A. de et al. (2002) Galectin-1 is overexpressed in nasal polyps under budesonide and inhibits eosinophil migration. Lab. Invest. **82:** 147–158

107 Hittelet A., Legendre H., Nagy N., Bronckart Y., Pector J. C., Salmon I. et al. (2003) Upregulation of galectins-1 and -3 in human colon cancer and their role in regulating cell migration. Int. J. Cancer **103:** 370–379

108 Nagy N., Bronckart Y., Camby I., Phillipart P., Lahm H., Kaltner H. et al. (2002) Galectin-8 expression decreases in cancer as compared to normal and dysplastic human colon tissue and acts significantly on human colon cancer cell migration. Gut **50:** 392–401

109 Camby I., Decaestecker C., Lefranc F., Kaltner H., Gabius H. J. and Kiss R. (2005) Galectin-1 knocking down in human U87 glioblastoma cells alters their gene expression pattern. Biochem. Biophys. Res. Commun. **16:** 27–35

110 Hikita C., Vijayakumar S., Takito J., Erdjument-Bromage H., Tempst P. and Al-Awqati Q. (2000) Induction of terminal differentiation in epithelial cells requires polymerization of hensin by galectin-3. J. Cell. Biol. **151:** 1235–1246

111 Moiseeva E. P., Williams B., Goodall A. H. and Samani N. J. (2003) Galectin-1 interacts with β1 subunit of integrin. Biochem. Biophys. Res. Commun. **310:** 1010–1016

112 Vanbenbrule F. A., Biucu C., Baldet M., Sobel M. E., Cooper D. N. W., Marschal P. , et al. (1995) Galectin-1 modulates human melanoma cell adhesion to laminin. Biochem. Biophys. Res. Commun. **209:** 760–767

113 Hadari Y. R., Arbel-Goren R., Levy Y., Amsterdam A., Alon R., Zakut R. et al. (2000) Galectin-8 binding to integrins inhibits cell adhesion and induces apoptosis. J. Cell. Sci. **113:** 2385–2397

114 Levy Y., Ronen D., Bershadsky A. D. and Zick Y. (2003) Sustained induction of ERK, protein kinase B, and p70 S6 kinase regulates cell spreading and formation of F-actin microspikes upon ligation of integrins by galectin-8, a mammalian lectin. J. Biol. Chem. **278:** 14533–14542

115 Debray C., Vereecken P., Belot N., Teillard P., Brion J. P., Pandolfo M. et al. (2005) Multifaceted role of galectin-3 on human glioblastoma cell motility. Biochem. Biophys. Res. Commun. **325:** 1393–1398

116 Matarrese P., Fusco O., Tinari N., Natoli C., Liu F. T., Semeraro M. L. et al. (2000) Galectin-3 overexpression protects from apoptosis by improving cell adhesion properties. Int. J. Cancer **85:** 545–554

117 Warrfield P. R., Makker P. N., Raz A. and Ochieng J. (1997) Adhesion of human breast carcinoma to extracellular matrix proteins is modulated by galectin-3. Invasion Metastasis **17:** 101–112

118 Cumpstey I., Carlsson S., Leffler H. and Nilsson U. J. (2005) Synthesis of a phenyl thio-beta-D-galactopyranoside library from 1,5-difluoro-2,4-dinitrobenzene: discovery of efficient and selective monosaccharide inhibitors of galectin-7. Org. Biomol. Chem. **3:** 1922–1932

To access this journal online:
http://www.birkhauser.ch