Published in final edited form as:

J Dermatol Sci. 2011 November ; 64(2): 85–91. doi:10.1016/j.jdermsci.2011.07.008.

Galectin-3 and the Skin

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Abstract

Galectin-3 is highly expressed in epithelial cells including keratinocytes and is involved in the pathogenesis of inflammatory skin diseases by affecting the functions of immune cells. For example, galectin-3 can contribute to atopic dermatitis (AD) by promoting polarization toward a Th2 immune response by regulating dendritic cell (DC) and T cell functions. In addition, galectin-3 may be involved in the development of contact hypersensitivity by regulating the migratory capacity of antigen presenting cells. Galectin-3 may act as a regulator of epithelial tumor progression and development through various signaling pathways, such as inhibiting keratinocyte apoptosis through regulation of the activation status of extracellular signal-regulated kinase (ERK) and activated protein kinase B (AKT). Galectin-3 is detected at different stages of melanoma development. In contrast, a marked decrease in the expression of galectin-3 is observed in non-melanoma skin cancers, such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Galectin-3 may play an important role in tumor cell growth, apoptosis, cell motility, invasion, and metastasis. Galectin-3 may be a novel therapeutic target for a variety of skin diseases.

1. Introduction

Galectins are a family of β -galactoside-binding lectins with one or two conserved carbohydrate-recognition domains (CRD) (Cummings and Liu, 2009). They are expressed in various human cell types and tissues as well as in many different organisms, including other mammals, sponges, fungi, nematodes, insects, and even viruses. To date, 17 mammalian galectins have been reported in the literature. A majority of them consist entirely of one CRD made of approximately 130 amino acids and a few others contain two homologous CRDs separated by a linker of up to 70 amino acids. Galectin-3 contains one CRD following a nonlectin region of about 120 amino acids made of tandem repeats of short proline/ glycine-rich sequences.

Although most galectins recognize galactose, they exhibit individual preferences in binding to galactose-containing bi- and oligo-saccharides (Hirabayashi et al., 2002). Some galectins

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bind to saccharides that are not galactose (for instance, galectin-10 exhibits no affinity for β -galactosides but instead binds to mannose (Swaminathan et al., 1999)).

Many single-CRD galectins are capable of forming homo-dimers and thus can be functionally bivalent with regard to binding to carbohydrate ligands. Double-CRD galectins are intrinsically bivalent with the presence of two carbohydrate-binding sites in a single polypeptide chain, although the two sites have different carbohydrate-binding specificity (Hirabayashi et al., 2002). Galectin-3 forms pentamers upon binding to multivalent carbohydrates, which involves self-association of the N-terminal non-lectin region (Ahmad et al., 2004). Galectins can thus form ordered arrays with cell surface glycoproteins containing multiple glyco-moieties that they bind to (Sacchettini et al., 2001). These complexes are referred to as “galectin lattices” (Fig. 1).

Many galectins are widely distributed in tissues, but a few are highly tissue specific. Galectin genes do not encode a classic signal sequence. The proteins are localized primarily in the cytoplasm and nucleus, although they can also be found in the extracellular space, possibly released by cells through a non-classical secretory pathway. The distribution of galectins between cytoplasm and nucleus depends on the cell types and proliferative states. For example, in senescent fibroblasts, galectin-3 is predominantly cytoplasmic, but in proliferating fibroblasts, it is mainly localized in the nucleus (Moutsatsos et al., 1987). Differential localization between the two compartments may be regulated by phosphorylation, as the phosphorylated form of galectin-3 is found in both compartments, whereas the unphosphorylated form is found exclusively in the nucleus (Cowles et al., 1990).

Galectins work extracellularly in an autocrine or paracrine manner to activate cells, mediate cell-cell and cell-extracellular matrix (ECM) interactions, and modify migration of inflammatory cells (reviewed in (Yang et al., 2008)). These are likely a result of cross-linkage of glycans on the cell surfaces because of their bivalency or oligovalency with regard to carbohydrate binding. The formation of galectin lattices on the cell surfaces mentioned above can result in modulation of the properties and responses of the receptors, such as lateral mobility and rate of endocytosis (reviewed in (Dennis et al., 2009)).

Galectins can also work intracellularly in a carbohydrate-independent manner to regulate functions such as apoptosis, migration, and inflammation (reviewed in (Liu et al., 2002; Yang et al., 2008)). In addition, they can be engaged in pre-mRNA splicing by functioning as components of spliceosomes (reviewed in (Haudek et al., 2010)), and regulate the expression of certain genes (Nakahara and Raz, 2007).

2. Role of galectin-3 in the biological responses of skin cells

Galectin-3 has a wide tissue distribution and is highly expressed in a variety of inflammatory and epithelial cells (reviewed in (Yang et al., 2008)). With regard to the skin, it is expressed in keratinocytes, hair follicles, sebaceous, and sweat glands (Konstantinov et al., 1994). It is also expressed by other resident cells in the epidermis and dermis, including melanocytes, dendritic cells, fibroblasts, and monocytes.

2.1. Keratinocytes

By immunofluorescence and immunohistochemistry, galectin-3 was found to be present abundantly in the cytoplasm of normal keratinocytes with perinuclear enhancement (Konstantinov et al., 1994). Galectin-3 is abundant in the more fully keratinized stratum malpighii (Konstantinov et al., 1994), but seems to be more limited suprabasally in the epithelium (Plzak et al., 2001). Galectin-3 is upregulated when human keratinocytes were

cultured for a few days after they became confluent, when the cells became more differentiated (Sarafian et al., 2006). Galectin-3 in the suprabasal layers of epidermis has been shown to be colocalized with desmosomal proteins (Plzak et al., 2001). These findings suggest that galectin-3 expression is associated with keratinocyte differentiation and maturation. Whether it plays a role in these processes is unknown.

One of the most extensively studied functions of galectin-3 is anti-apoptosis. Keratinocyte apoptosis is a highly controlled and important process in epidermal homeostasis. The study of the role of galectin-3 in UVB irradiation-induced apoptosis in mouse keratinocytes revealed a means by which galectin-3 may modulate apoptosis in this cell type. Wild-type keratinocytes show a transient galectin-3 mRNA upregulation after ultraviolet-B (UVB) irradiation. Both *in vivo* and *in vitro*, galectin-3 deficient ($gal3^{-/-}$) keratinocytes were more sensitive to UVB-induced apoptosis, as well as other apoptotic stimuli than wild type cells. The increase in apoptosis was attributed to an increase in ERK and c-Jun N-terminal kinase (JNK), but a decrease in AKT activation after UVB irradiation. Thus, galectin-3 may play a role in other apoptosis-related responses of keratinocytes through suppressing ERK activation and enhancing AKT activation (Saegusa et al., 2008). Recombinant galectin-3 has been shown to induce keratinocyte migration possibly through an extracellular interaction with beta4 integrin, EGFR, and laminin on the keratinocyte matrix (Kariya et al., 2010).

2.3. Fibroblasts

The expression of galectin-3 in fibroblasts has been associated with the growth status of these cells. In serum-stimulated fibroblasts, the young proliferating cells had increased galectin-3 expression compared to high-passage quiescent cells and those cells with defective replication (Hamann et al., 1991). Recombinant galectin-3 has been shown to be a strong growth stimulant of colonic fibroblasts (Lippert et al., 2007). Whether it has a similar effect on skin fibroblasts is not known and whether endogenous galectin-3 functions as an autocrine or paracrine growth stimulant remains to be determined.

2.4. Antigen-presenting cells

Galectin-3 is present on the surface of Langerhans cells (LCs) as well as in Birbeck granules in this cell type (Wollenberg et al., 1993). As human dendritic cells (DCs) mature, their surface glycosylation pattern changes and more galectin-3 can bind to the cells (Bax et al., 2007). The functional significance of this remains to be investigated. By comparing DCs from $gal3^{+/+}$ and $gal3^{-/-}$ mice, endogenous galectin-3 was found to have a suppressive effect on the production of IL-12 by DCs, which is a potent Th1-polarizing cytokine (Bernardes et al., 2006). Similarly, endogenous galectin-3 in DCs was found to suppress the magnitude of T-lymphocyte priming induced by DCs (Breuilh et al., 2007). Compared to wild type DCs, $Gal3^{-/-}$ bone marrow-derived DCs have a defective migratory response to chemokines *in vitro* and reduced migration to lymph nodes *in vivo* (Hsu et al., 2009b), suggesting that galectin-3 is important for DC migration. In macrophages, endogenous galectin-3 was found to translocate to the phagosomes in cells that have engulfed red cells and contribute to Fc γ R-mediated phagocytosis of red cells (Sano et al., 2003). Extracellular galectin-3 can act as an opsonin to enhance phagocytosis of apoptotic neutrophils by macrophages (Karlsson et al., 2009).

The functions of galectin-3 described above are summarized in Figure 2.

3. Galectin-3 and inflammatory skin diseases

The roles of galectin-3 in immunity and inflammation have been extensively studied (reviewed in (Liu and Rabinovich, 2010; Yang et al., 2008)). These include induction of cell activation, regulation of cellular homeostasis, and promotion of cell adhesion as well as cell

migration. Extracellular galectin-3 induces apoptosis in activated human T cells, as demonstrated by using recombinant proteins added to the cells. However, endogenous galectin-3 is anti-apoptotic in human T and B cell lines through an intracellular action (Hsu et al., 2006). Extracellular galectin-3 can form lattices with the T-cell receptor (TCR) complex and negatively regulate TCR-mediated signal transduction (Demetriou et al., 2001). Endogenous galectin-3 suppresses TCR-mediated mouse CD4⁺ T-cell activation by functioning intracellularly at the immunological synapse (Chen et al., 2009).

With regard to inflammation, galectin-3 has been shown to activate a number of lymphoid and myeloid cells, function as a chemoattractant for human monocytes and macrophages (Sano et al., 2000), and promote cell adhesion of myeloid cells (Yang et al., 2008). Moreover, it plays a critical role in alternative macrophage activation (MacKinnon et al., 2008). In addition, intracellular galectin-3 positively regulates the responses of a number of other immune cell types, including mediator release by mast cells (Chen et al., 2006). *In vivo* studies using galectin-3-deficient mice support the notion that galectin-3 promotes inflammatory responses in mouse models (reviewed in (Yang et al., 2008)).

3.1. Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin condition that involves an inherited epidermal barrier defect which may allow for greater penetration by allergens and irritants. There is increasing evidence that there is a predominant Th2 cytokine milieu in the initiating stages of AD and a mixed Th1 and Th2 pattern in chronic lesions (Ong and Leung, 2006).

IgE-associated atopic eczema/dermatitis syndrome (AEDS) contains abnormal B-cells that are surface IgE-positive (sIgE+) and produce IgE spontaneously in culture. It was found that IgE production in patients AEDS was amplified by PMNs from these patients, but not healthy controls, and the authors proposed that galectin-3 released by PMNs is contributory. They showed IgE release was enhanced by the addition of galectin-3 to the cultures of AEDS B cells admixed with PMNs from healthy controls. These results suggest that galectin-3 can enhance PMN-induced IgE synthesis by B cells that are already committed to IgE production and thus, galectin-3 may be involved in the hyperactive immune response in AEDS (Kimata, 2002).

Saegusa et al. (Saegusa et al., 2009) looked at the effects of endogenous galectin-3 in the development of an allergic inflammatory response in a mouse model of AD induced by repeated epicutaneous sensitization with ovalbumin (OVA). Galectin-3 expression in the epidermis was upregulated after sensitization. Gal3^{-/-} mice had reduced epidermal thickening, lower eosinophil infiltrates, lower serum IgE, a lower Th2, but higher Th1 response compared to gal3^{+/+} mice. In addition, *in vitro* gal3^{-/-} dendritic cell (DC) presentation of OVA peptide to T cells resulted in a Th1-biased response, which is likely related to galectin-3's IL-12-suppressive activity in DCs. Furthermore, mice that received T cells from gal3^{-/-} OVA-specific T cell receptor transgenic mice developed a lower Th2 response and lower skin inflammation after OVA exposure than mice that received gal3^{+/+} T cells. These results suggest that galectin-3 is required for the development of the Th2 inflammatory response to epicutaneously-introduced antigens through its effects on both DCs and T cells (Saegusa et al., 2009). These results along with the information mentioned above suggest that galectin-3 is a pro-inflammatory mediator of skin inflammation in atopic skin disease.

3.3. Contact dermatitis

Recent studies on the effects on nickel have unlocked the possibility of galectin-3 involvement in the allergic effects of nickel. Human epidermal keratinocytes are the primary

target for nickel. Using in silico data analysis it was found that 134 genes are regulated by nickel. By looking at the functional categories of the regulated genes, it was suggested that nickel inhibits apoptosis, promotes the cell cycle, and induces synthesis of extracellular matrix proteins and proteases. One of the proteins that nickel exposure suppresses in keratinocytes is galectin-3 (Gazel et al., 2008). Endogenous galectin-3 positively regulates allergic contact dermatitis in mice, as determined by comparing *gal3^{-/-}* mice and wild-type mice (Hsu et al., 2009b). This may be related to the role of galectin-3 in controlling migration of DCs, as described above. The contribution of galectin-3 in other functional aspects of DCs or in other cell types involved in contact sensitivity cannot be excluded.

3.3. Psoriasis

Relatively few studies have examined the correlation between psoriasis and galectins. Lacina et al. (Lacina et al., 2006) investigated the expression of galectin-1, -3, -7 and their glycoligands in psoriatic skin compared to normal skin. Compared to normal epidermis, there is much lower galectin-3 expression in psoriatic epithelium. However, there was strong expression of galectin-3 and galectin-3-reactive glycoligands in the capillary epithelia of psoriatic dermis. It was suggested that development of psoriasis may be related to the effects of galectin-3 and galectin-3-reactive glycoligands on dermal capillaries in creating some sort of rearrangement of the capillary network and recruitment of inflammatory cells (Lacina et al., 2006).

Figure 2 summarizes the role of galectin-3 in skin inflammatory diseases.

4. Roles of galectin-3 in skin cancers

There is a great deal of information on the role of galectin-3 in tumor growth, progression, and metastasis (reviewed in (Liu and Rabinovich, 2005)). There is evidence that its expression is necessary for the initiation of the transformed phenotype of tumors, possibly related to its ability to interact with oncogenic K-ras (Elad-Sfadia et al., 2004). The most extensively studied function of galectin-3 is its inhibition of apoptosis in a variety of tumor cell types exposed to diverse apoptotic stimuli. In this regard, this protein may play a key role in apoptosis in the tumor suppressor p53 pathway, because the action of the latter involves repression of galectin-3 (Cecchinelli et al., 2006). Galectin-3 may also be engaged in tumor cell cycle progression by controlling the levels of some key regulators, such as cyclin D₁ and c-myc (Shimura et al., 2005). In addition, galectin-3 can affect invasiveness of tumor cells by promoting cell migration and affect the tumor microenvironment, by promoting angiogenesis and fibrosis (reviewed in (Yang et al., 2008)). Finally, tumor-associated galectin-3 may contribute to tumor immune escape by killing tumor-targeting T cells or by rendering them nonreactive (reviewed in (Hsu et al., 2009a)). Elevated galectin-3 expression is associated with increased anchorage-independent growth, homotypic aggregation, and tumor cell colonization, which are all attributes of cancerous cells (Lotan and Raz, 1988). Tumor cells transfected to increase galectin-3 expression have been shown to have higher rate of metastasis compared to control transfectants when inoculated into mice (Bresalier et al., 1998). Galectin-3 expression is variable depending on the cancer studied, even within epithelial neoplasms (Kapucuoglu et al., 2009; Konstantinov et al., 1994; Mollenhauer et al., 2003). In melanoma, galectin-3 tends to be up regulated; however in non-melanoma skin cancers it is down regulated and expression seems to correlate with cell maturity.

4.1. Melanoma

Although investigation into the mechanism of galectin-3 on melanoma cells shows variable results, the general consensus of all the studies is that galectin-3 has a regulatory effect on

melanoma progression and metastasis. In general, galectin-3 expression is upregulated in melanoma cells and nevi compared to normal melanocytes (Prieto et al., 2006). However, there is a debate as to the level of expression at various tumor stages.

In one study, increased levels of galectin-3 and an increase in the nuclear to cytoplasmic ratio of galectin-3 were noted in metastatic lesions compared to primary lesions (Prieto et al., 2006). The authors also noted a correlation between the nuclear expression of galectin-3 and prognosis. Another study by the same group found that melanoma cells with silenced galectin-3 had decreased tumorigenic potential with less tumor marker expression (Mourad-Zeidan et al., 2008).

Similarly, in another study, galectin-3 was found to be expressed in all the benign and malignant melanocytic lesions and while galectin-3 was present only in the cytoplasm in benign lesions, it is present in both the cytoplasm and nucleus (nucleocytoplasmic pattern) in a large percentage of cases (42.9%) of melanoma. The intensity of galectin-3 staining was significantly higher in malignant lesions compared to benign lesions. The nucleocytoplasmic pattern is related to poorer prognosis, although the difference did not reach statistical significance (Abdou et al., 2010).

In contrast to the studies above, a xenograft melanoma model using human melanoma cell lines found that the expression of galectin-3 was lower in more advanced lesions and correlated inversely with aggressiveness, suggesting that low levels of galectin-3 may act as a trigger for aberrant proliferation (Vereecken et al., 2005). The authors suggested that the decreased levels of galectin-3 in more advanced lesions may also be a mode for metastasis by decreasing interactions of melanoma cells with the ECM and promoting a mode for the malignant cells to detach from the basement membrane and enter the circulation.

The serum levels of galectin-3 were noted to be higher in melanoma patients (Iurisci et al., 2000; Vereecken et al., 2006). It is unknown whether the galectin-3 is produced by the melanoma cells or inflammatory cells. The elevated galectin-3 levels are correlated with the biological aspects of tumor behavior associated with metastatic phenotypes (Iurisci et al., 2000). The levels are also associated with other inflammatory indicators, such as C-reactive protein and lactate dehydrogenase levels, as well as the level of galectin-3 immunostaining in cutaneous metastases (Vereecken et al., 2006). Interestingly, in a recent study, melanoma patients were found to have autoantibodies against galectin-3 (Forgber et al., 2009). Thus, serum galectin-3 or autoantibodies may be used in the future for melanoma staging, prognosis, and follow-up.

There are a number of possible mechanisms by which galectin-3 may regulate the melanoma tumor development and metastasis. The metastatic potential of mouse melanoma cells was shown to correlate with the extent of galectin-3 expression on the cell surface (Raz et al., 1987). Melanoma has been shown to interact with elastin and matrix proteins containing polylactosamine chains, such as fibronectin, laminin, elastin degradation products (EDPs), and integrins (Lapis and Timar, 2002). Typically, high quantities of elastin have been associated with more advanced stages of melanoma. Elastin-derived peptides have been shown to promote invasion of melanoma cells in vitro, through inducing expression of CXCR-4 and CXCL-12 chemokines, lymphangiogenic VEGF-C, and elastin-degrading matrix metalloproteinases, as well as increased attachment through adhesion molecule expression. Importantly, galectin-3 has been shown to mediate the effects of these peptides, as demonstrated by using a neutralizing anti-galectin-3 antibody (Pocza et al., 2008). Galectin-3 has also been shown to mediate homotypic cell adhesion and aggregation by bridging through branched soluble complementary glycoconjugates (Inohara and Raz, 1995) and galectin-3-binding protein (Inohara et al., 1996).

Contrary to the findings above, one study showed that extracellular galectin-3 exerts an inhibitory effect on tumor cell adhesion to the ECM (Ochieng et al., 1998) and another study failed to note galectin-3 modulation of adhesion of melanoma cells to laminin (van den Brule et al., 1995). Thus, although galectin-3 binds to laminin, it may not be a key direct mediator or receptor of cell adhesion to laminin, but may instead act as a regulator of other molecular interactions like those mentioned above.

4.2. Non-melanoma skin cancers

The most common types of skin cancer are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC is thought to arise from progenitor cells in the basal layer of the epidermis. SCC is a malignant proliferation of the keratinocytes of the epidermis. In general, there is a down regulation of galectin-3 in non-melanoma skin cancers compared to non-neoplastic epidermis (Kapucuoglu et al., 2009).

In BCC and SCC, there is greater staining of galectin-3 in the central parts of the tumor islands that contain more differentiated and keratinized cells. Positively stained cells did not show surface reactivity but rather slight cytoplasmic staining and the surrounding stroma was negative. In correlation with this, well-differentiated SCCs had greater overall staining than less differentiated. Additionally, keratoacanthomas showed similar staining to SCC and the least differentiated outer cell layers were invariably negative (Konstantinov et al., 1994).

A more recent article looked at galectin-3 expression in SCC and BCC and correlated it with grade of differentiation and tumor size. It was noted that cytoplasmic immunoreactivity of galectin-3 was greater than nuclear in all cases. In SCC there was a positive correlation between cytoplasmic staining intensity and tumor size. The cytoplasmic galectin-3 in SCC may contribute to tumor size through its anti-apoptotic activity. However, in BCC there was no correlation between tumor size and galectin-3 expression. There was no galectin-3 expression in the more developed keratin pearls. There was also no relationship between galectin-3 expression and tumor differentiation and lymph node metastasis (Kapucuoglu et al., 2009).

Galectin-3 may affect tumor development and progression through interactions with regulatory genes. DMBT-1 is a potential tumor suppressor gene that codes for an extracellular protein that mediates protein-protein interactions and may trigger cell differentiation. Inactivation of DMBT1 may be required for tumorigenesis (Mollenhauer et al., 2002). DMBT1 and galectin-3 interaction in the ECM may promote cellular differentiation which could allow for a cycle of non-malignant, normal growth. Skin tumors of epithelial origin exhibited a down regulation of both DMBT1 and galectin-3 in a vast majority of samples. The interaction of galectin-3 and DMBT1 may play a role in the development of epithelial skin cancers. This also suggests that galectin-3 may have tumor suppressive effects (Mollenhauer et al., 2003).

Figure 3 summarizes the roles of galectin-3 in pathogenesis of skin cancers.

5. Conclusions

Galectin-3 has been shown to contribute to fundamental cellular responses. In the skin, it plays critical roles in immune and inflammatory responses as well as cancer development and progression, by functioning in epithelial cells, immune cells, and tumor cells. Therapies targeting galectin-3 may prove beneficial for treatment of these skin diseases discussed in this review. It should be emphasized that activities demonstrated by using recombinant galectin-3 added to cells may not represent the functions of endogenous galectin-3 in that particular cell type. On the other hand, the ones demonstrated by using galectin-3 knockout

mice do represent the functions of endogenous galectin-3. Continued studies of this strain of mice, as well as mice in which galectin-3 is deleted conditionally and in a tissue-specific fashion, are important for a more comprehensive understanding of the functions of galectin-3 in the skin.

In addition, while galectin-3 may have extracellular functions such as cell/cell and cell/ECM interaction, as well as binding to cell surface ligands to initiate signal transduction, it clearly functions inside the cell. The latter may be related to its interaction with intracellular unglycosylated proteins. Additional investigations are necessary to further clarify the dual intra- and extra-cellular functions of galectin-3, as well as other galectins.

Finally, before galectin-3-based therapeutic agents can be extrapolated to clinical settings, determination of whether the functions demonstrated for this galectin in vitro are operative in vivo. It is also critical to determine whether galectin-3 exerts the demonstrated functions through intra- or extra-cellular action. This will determine whether the inhibitors used should target the extra- or intra-cellular space.

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Figure 1. Galectins and lattice formation of galectin-3

A. Galectin-3 is the only chimeric galectin that consists of one carbohydrate recognition domain (CRD) linked to a flexible non-lectin domain made of tandem repeats. Other galectins are made of either one CRD or two CRDs. B. Galectin-3 forms pentamers upon binding to multivalent carbohydrates and can form lattices with multivalent glycoconjugates.

Figure 2. Role of galectin-3 in skin inflammatory diseases

Galectin-3 can affect a broad range of inflammatory responses in the skin by functioning in epithelial cells and immune cells, either in an extracellular or intracellular fashion. Keratinocyte apoptosis is an important control mechanism in the maintenance of epidermal homeostasis, and is inhibited by galectin-3. Galectin-3 contributes to dendritic cells (DC)/macrophage (Mφ) chemotaxis and phagocytosis. In addition, endogenous galectin-3 negatively regulates T cell receptor (TCR)-mediated signal transduction in T cells, and also protects T cells from apoptosis. Endogenous and exogenous galectin-3 promotes mast cell activation and degranulation. Further, galectin-3 drives a Th2-polarized response and promotes allergic skin inflammation through its control of DCs and T cells. Abbreviation: CD: contact dermatitis; AD: atopic dermatitis; UVB: ultraviolet B; Ag: antigen; LC: Langerhans cell; MC: mast cell; APC: antigen presenting cell

Galectin-3:**Inhibit apoptosis: via regulation by P53 pathway****Promote tumor progress: via interaction with K-ras****Promote immune escape by inducing anergy in cytotoxic T cells****Promote angiogenesis and tumor cell migration****Melanoma:****galectin-3 expression increased****galectin-3 promotes cell adhesion, invasiveness and metastasis; decreases melanoma:extracellular matrix interaction****Non-melanocytic skin cancer: Squamous-cell carcinoma****Increased galectin-3 expression****cytoplasmic galectin-3 is correlated with tumor size****Figure 3. Galectin-3 and skin cancer**

Galectin-3 may have important roles during different steps of tumorigenic processes, including tumor cell transformation, cell-cycle regulation, and apoptosis. Galectin-3 can mediate neoplastic transformation by interacting with oncogenic K-ras. Galectin-3 may be an effector molecule downstream of tumor suppressor p53, and inhibits apoptosis in a range of tumor cell types exposed to diverse apoptotic stimuli. Of note, galectin-3 can affect tumor metastasis by modulating tumor cell migration and motility, and promote angiogenesis by enhancing endothelial cell migration. Furthermore, galectin-3 may promote tumor immune escape by killing tumor-targeting cytotoxic T lymphocytes (CTLs) or by rendering them nonreactive. In melanoma, galectin-3 tends to be up-regulated, however, in non-melanoma skin cancers, its expression is down-regulated and seems to correlate with cell maturity.