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REVIEW

Galectins 7 and 9 in Dermatology: Current knowledge and future perspectives

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ABSTRACT

Galectins constitute a family of β-galactoside-binding proteins (lectins) that are widely distributed in nature occurring in mammals, sponges, fungi, nematodes, insects and viruses. Galectins are involved in fundamental cellular processes in human skin and other tissues. They exert biological effects of considerable importance through interactions with cytoplasmic and nuclear proteins, as well as with components of cell surface and extracellular matrix.

In this paper we summarize current knowledge on the expression of galectins 7 and 9 in normal and diseased human skin and present the future perspectives of the use of these galectins or their antagonists/inhibitors in the diagnosis, prognosis and treatment of cutaneous disorders.

KEY WORDS: *Epidermis; β-galactoside-binding proteins; galectin 7; galectin 9*

INTRODUCTION

Galectins constitute a family of β-galactoside-binding proteins, most members of which possess one or two unique structures termed "conserved carbohydrate-recognition domains" (CRDs). These proteins are expressed in cells and tissues of humans and diverse organisms and reveal a high binding affinity for β-galactose in glucoconjugates, which depends on the structure of the latter and the possible modifications of galactose residues, such as sialylation, fucosylation and sulfation.[1,2] Seventeen mammalian galectins (12 occur in humans) have so far been identified, most of which consist of one CRD with about 130 amino acids, whereas a few others contain two homologous CRDs separated by a linker of up to 70 amino acids.[1]

Based on their structural properties, galectins can be classified into three major types (Figure 1):

a) ***The prototypical type*** (galectins 1, 2, 5, 7, 10, 11, 13, 14, 15, 16 and 17) which contains one single CRD that may associate to form homodimers.[3]
b) ***The tandem-repeat type*** (galectins 4, 6, 8, 9 and 12) in which at least two CRDs occurring within a single peptide linked by a small peptide domain possess different carbohydrate-binding affinities.[2-4]

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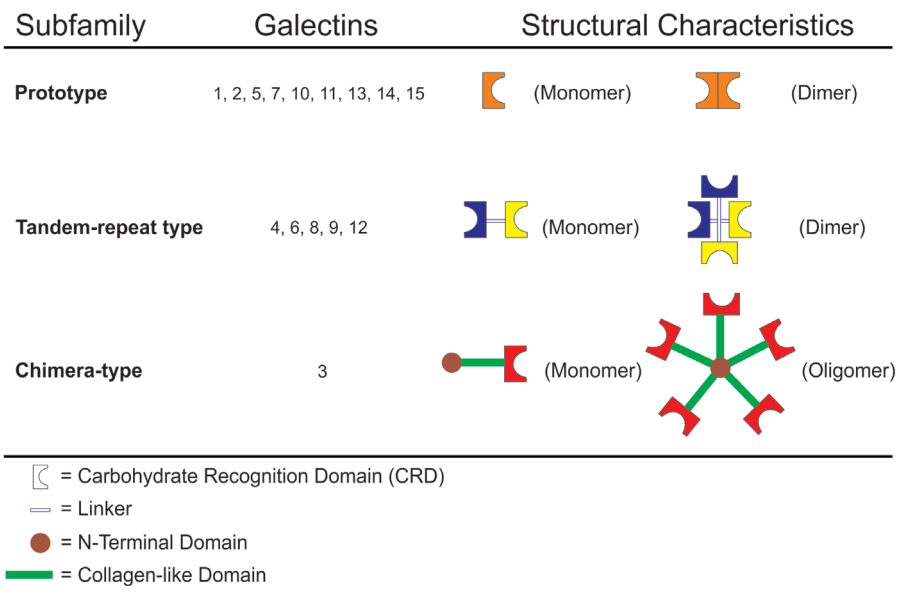

FIGURE 1. Classification of galectins.

c) ***The chimera type*** with galectin 3 as its sole representative. Apart from one CRD, this galectin contains a proline-rich collagen-like domain and a N-terminal domain.[2,3]

Galectins are synthesized in the ribosomes, are present in the cytoplasm and are translocated to the nucleus and other cellular compartments.[5] Additionally, subsequent to their secretion via non classical pathways[6], galectins can be found at the cell surface and in the extracellular environment.[7] The expression and the distribution of galectins in the cytoplasm and the nucleus mainly depend on the type and the proliferative state of cells. Galectins are involved in a wide variety of significant molecular and cellular processes in both cutaneous and extracutaneous tissues and in the pathogenetic mechanisms of diverse disorders.[8]

The purpose of this paper is to present current knowledge with regard to the expression of galectins 7 and 9 in normal and diseased human skin and to summarize the future perspectives of the use of these galectins and their antagonists/inhibitors in the diagnosis, prognosis and treatment of cutaneous disorders. The overview of the available data is based on the results of an electronic literature research that was conducted on the MEDLINE and SCOPUS databases until June 2018 using various combinations of the primary keyword "Galectins" with relevant terms, the most important of which were: keratinocytes, Langerhans cells, Merkel cells, melanocytes, lymphocytes, macrophages, skin, human adult epidermis, human embryonic epidermis, keratinization, infection, inflammation, immune response, cutaneous angiogenesis, melanoma, cutaneous neoplasms, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, actinic keratosis, xanthoma, nevi, Bowen's disease, tumor invasion and metastasis.

GALECTIN 7

Galectin 7 (Gal 7) is a 14kDa one-CRD prototypical galectin encoded by the *LGALS7* gene that is located on chromosome 19. Gal 7 is mainly expressed in squamous stratified epithelia (keratinized or not), the outer root sheath of the hair follicle, the oral epithelia, the lips, the esophagus, the cornea, the Hassall's corpuscles of the thymus and in myoepithelial cells from the mammary epithelia.[9]

Gal 7 functions extracellularly as a conventional galectin, whereas intracellularly it is localized in the nucleus, the cytoplasm and the mitochondria. In the latter, it acts in a Bcl-2-dependent manner, sensitizing them to the apoptotic signal.[10,11] In view of its proapoptotic activity, Gal 7 is regarded as a new molecular target for enhancement of the intrinsic apoptosis pathway.[11] In more recent studies, however, it was found that Gal 7 is capable of causing not only promotion but also suppression of the apoptotic process depending on the cell type, the conditions of the microenvironment and the nature of the apoptotic stimuli.[12]

Gal 7 is secreted by proliferating, quiescent and differentiated keratinocytes via a non-classical secretory pathway and is capable of suppressing proliferation in various cell lines.[9,12] In Gal 7-null mice, the lack of expression of this galectin is associated with increased cell proliferation after epidermal injury or cutaneous irradiation with UVB.[13] Tumor suppressor gene p53 induces a marked upregulation of Gal 7 expression,[14] whereas in human keratinocytes lacking the wild type p53 no induction of Gal 7 expression upon UVB irradiation is observed.[15]

The significance of Gal 7 as a differentiation marker of epidermal keratinocytes remains in dispute. Since this ga-

lectin is expressed in and secreted by proliferating basal and differentiated suprabasal keratinocytes,[16-18] it is regarded by some authors as a marker of stratified epithelia but not as a differentiation marker.[19] Nevertheless, its downregulation in keratinocyte cultures upon addition of retinoic acid and the increase of Gal 7 mRNA in relation to cell density[14,16] suggest that this galectin may also be associated with epidermal keratinocyte differentiation. More recently, Chen et al.[20] reported that Gal 7 is capable of regulating the proliferation and differentiation of epidermal keratinocytes through the JNK1-miR-203-p63 pathway.

Gal 7 exerts distinct effects on cellular adhesion and migration, processes of particular importance for wound healing, cancer progression and metastasis. It interacts with E-cadherin of adherent junctions in keratinocytes binding directly to its extracellular domain and leads to E-cadherin stabilization.[13,19] Interestingly, both absence or overexpression of Gal 7 cause an impairment of adherent junction-mediated adhesion.[12,19] Gal 7 may also be capable of regulating cell adhesion to extracellular matrix through interaction with β1-integrin and enhancement of matrix metalloproteinases expression.[21-23]

NORMAL HUMAN SKIN

There are no data with regard to the occurrence of Gal 7 in the embryonic human skin. In the adult normal human skin immunoreactivity for this galectin is found along the cell membrane of the cells in the basal and suprabasal layers, whereas the horny layer shows no Gal 7 expression.[24] Distinct Gal 7 immunoreactivity is found in the basal cells of hair follicles, the resident macrophages, the collagen fibrils of the dermis, the Langerhans cells, the extracellular matrix, the fibroblasts and the capillary walls.[16,18,24-27] Interestingly, Lacina et al.[28] found a positive cytoplasmic immunoreactivity for Gal 7 in the keratinocytes in the basal and suprabasal layers but also in the stratum corneum of normal human epidermis with no signs of nuclear expression. Recently, Choi et al.[29] found immunoreactivity for Gal 7 only in the cytoplasm of keratinocytes in normal epidermis and provided evidence suggesting that Gal 7 is a sensitive marker for differentiated and active keratinocytes in which its expression reveals a progressive age-dependent decrease.

CUTANEOUS NEOPLASMS:

A. Epithelial

Data on the expression of Gal 7 in cutaneous epithelial neoplasms are conflicting and exclusively derived from studies on head and neck cancer. Magnaldo et al.[18] detected immunoreactivity for Gal 7 in all cell layers of basal cell carcinomas (BCCs), although the labeling was less pronounced, as compared to that of normal epidermis; the intensity of Gal 7 expression was lower in the basal and first suprabasal cell layers especially in BCCs.[18] On the contrary, Cada et al.[27] found no immunoreactivity for this galectin in BCCs.

Gal 7 was barely detected by Magnaldo et al[18] in squamous cell and spindle cell carcinomas, whereas other research groups found significantly high expression of this galectin in squamous cell carcinomas (SCCs) of the tongue, the buccal mucosa and the esophagus and suggested that Gal 7 may be involved in the mechanisms of oral carcinogenesis and may be regarded as marker of biological behavior and tumor progression.[27,30-32] Indeed, in oral SCCs, Gal 7 expression correlates with the histological malignancy grading system. In cultures of oral cancer cell lines, downregulation of this galectin results in a decrease of cell migration and invasion, whereas its overexpression exerts the opposite effects.[12,33]

B. Lymphomas

Moisan et al.[34] were the first to report that upregulation of galectin-7 in murine lymphoma cells is associated with their progression toward an aggressive phenotype. Demers et al.[35] reported that stable transfection of lymphoma cells with a plasmid encoding antisense Gal 7 cDNA caused a significant inhibition of dissemination and invasion of lymphoma cells to peripheral organs. Moreover, inhibition of Gal 7 in aggressive lymphoma cells correlates with the decrease in their invasion in target organs and the reduced expression of *matrix metalloproteinase-9,* which is known to be induced by Gal 7 in mouse and human lymphoma cells.[36] These authors also found an upregulation of Gal *7* levels in most investigated B-cell lymphoid malignancies but not in normal B lymphocytes. This upregulation of Gal 7 in lymphoma cells does not depend on p53 but is rather related to alterations in DNA methylation.[37] Based on their findings, these authors suggested that Gal 7 may serve as a potential therapeutic target in the treatment of lymphoid malignancies.

C. Melanomas

Gal 7 at the mRNA level was detected in more than 90% of skin biopsies obtained from patients with nevi; however, in situ labeling showed that Gal 7 immunoreactivity in these biopsies was likely due to that of the surrounding keratinocytes. Gal 7 expression was rarely found in skin biopsies derived from patients with malignant melanoma.[38] Gal 7 caused a reduction in the motility of B16F1 experimental melanoma cells, an increase in their resistance to apoptosis and an upregulation of early growth response protein 1 (EGR-1). Gal 7 ectopic expression was not capable of affecting either the growth of the tumors induced by the injection of B16F1 or their metastasis to the lungs.[38]

MISCELLANEOUS:

Cutaneous amyloidosis

It is well known that Gal 7 is a component of amyloid fibrils and contains considerable amounts of β-sheet structure. Miura et al.[39] detected this galectin by immunoblot assay in the water-soluble fractions prepared from the lesional skin of patients

with primary localized cutaneous amyloidosis. Moreover, they found Gal 7 immunoreactivity in tumor-associated localized cutaneous amyloidosis, whereas the dermis in the apparently normal skin of the patients was negative for this galectin.

Since Gal 7 is overexpressed in apoptotic keratinocytes and amyloid deposit is related to keratinocyte apoptosis, Gal 7 was considered as a possible candidate amyloidogenic protein.[39] Interestingly, the findings of the study of Ono et al.[40] provided evidence suggesting that in primary localized cutaneous amyloidosis (PLCA) the mechanism of amyloidogenesis includes the following steps: a. Induction of Gal 7 expression and activation of proteases related to the apoptotic process. b. Release of tryptic peptides at neutral conditions. c. Aggregation of amyloidogenic peptides in acidified pH that is modulated by Gal 7 peptides, actin and cytokeratins and d. Formation of amyloid fibrils by deposition of Gal 7 fragments. Further studies are now warranted to define the nature of Gal 7 peptides that participate in cutaneous amyloidogenesis and to answer the question as to whether this galectin might be a useful therapeutic target for the management of PLCA.

Wounds and scars

In patients with hypertrophic scars Gal 7 is markedly downregulated in both the skin and the serum.[41] The intensity of Gal 7 immunoreactivity in scars is localized along the cytoplasmic membrane of the basal and suprabasal cells and in the extracellular space of the papillary dermis, as well.[41] By means of ablative laser treatment, Cho et al (2013)[41] induced wound healing in healthy control tissue and demonstrated an uniformly intensive cytoplasmic staining of keratinocytes in the epidermis and the follicular outer sheath; during wound healing, they found a strong cytoplasmic membrane immunoreactivity of keratinocytes for Gal 7 at days 3, 5, 14 and 21 and of the upper papillary dermis at days 1, 3 and 10. Based on their findings, these authors suggested that the observed differences between control skin and hypertrophic scars with regard to the expression and subcellular/extracellular distribution of Gal 7 indicate that this galectin may play an important role in the pathogenetic mechanisms underlying the unbalanced scar formation.

In experimental studies it has been shown that Gal 7 can also regulate the migration of epithelial cells during wound healing subsequent to epidermal injury.[42] Indeed, re-epithelialisation in Gal 7-null mice was delayed, as compared to that seen in wild type mice without any difference in cell proliferation between the two groups. These findings indicate that the effects of Gal 7 on epidermal wound healing are due to the induced enhancement of keratinocyte migration and are not related to cell proliferation. This view is supported by the results of recent in vitro studies that showed a decrease in migration speed and efficiency in galectin-7-depleted keratinocytes (HaCaT cells).[19] Further studies are now warranted to assess the possible therapeutic potential of Gal 7 in the management of cutaneous wounds.

GALECTIN 9

Human galectin 9 (Gal 9) is a 34-39 kDa tandem-repeat type protein encoded by the *LGALS9* gene, that is located on chromosome 17q11.2.[43] Gal 9 contains two non-homologous N- and C-terminal CRDs connected by a linker peptide.[44] Gal 9 is found in a wide spectrum of human tissues and cell types including the skin, liver, spleen, small intestine, thymus, kidneys, lung, cardiac and skeletal muscles, brain, pancreas, placenta, prostate, colon, lymph nodes and peripheral blood leukocytes.[45]

Gal 9 reveals extracellular and intracellular distribution.[46] Extracellular Gal 9 is released from diverse cells via the non-classical pathways and can mediate, among others, processes such as cell adhesion and cell surface recognition, cell aggregation, cell-cell and cell-extracellular matrix interactions, migration, chemoattraction, receptor endocytosis, lipid recycling and raft clustering.[43,47] Intracellular Gal 9 can mediate mechanisms underlying signal transduction, development, growth, immune response and apoptosis.[48] Furthermore, this galectin is capable of regulating differentiation[45] and proliferation in diverse cell types[49] and of inducing concentration-dependent immunomodulation particularly through apoptosis of specific T cell subpopulations that are associated with autoimmunity, inflammation and graft rejection.[50,51]

NORMAL HUMAN SKIN

To the best of our knowledge, no data are available so far on the expression of Gal 9 in human embryonic skin. In normal adult human skin Cada et al.[27] observed a strong Gal 9 immunoreactivity in the keratinocytes of the basal layer and a weak one in those of the suprabasal layers. A weak positive Gal 9 immunoreactivity was also observed by de la Fuente et al.[52] in epidermal keratinocytes, Langerhans cells and dendritic cells of normal human skin, whereas dermal fibroblasts strongly expressed this galectin.[44]

CUTANEOUS AND SYSTEMIC DISORDERS:

Psoriasis

Although psoriasis represents the most common keratinization disorder, data on the expression of galectins in psoriatic lesions and their possible involvement in the pathogenetic mechanisms of this disease are sparse. De la Fuente et al.[52] found no significant differences between the lesional and the apparently normal skin of psoriatic patients and the skin of healthy controls with regard to the levels of Gal 9 mRNA expression. Recently, Igawa et al.[44] reported that there is a weak expression of Gal 9 in keratinocytes obtained from the

middle and upper layers of psoriatic epidermis, whereas dermal fibroblasts reveal a significant expression of this galectin.

Gal 9 is a physiological ligand of Tim-3, a cell surface molecule preferentially expressed on Th1 and Th17 cells.[53] In psoriasis, the expression of Tim-3 on these cells is impaired allowing them to escape from Tim-3-mediated negative regulatory system and to contribute to the pathogenesis of this disease.[54] Niwa et al.[55] developed a stable form of Gal 9 that is resistant to natural proteolytic inactivation and administered it to the IL-23-induced psoriatic mouse model. In the Gal 9-treated animals they observed a marked reduction of epidermal thickness, dermal cellular infiltrate and of the levels of IL-17 and IL-22 in the lesional skin. Although these experimental findings cannot be directly extrapolated to the human conditions, they do support, however, the hypothesis that Gal 9 may be a novel and promising agent for the treatment of psoriasis and other cutaneous disorders with Th1 and Th-17 mediated skin inflammation.[55]

Atopic dermatitis

Atopic dermatitis is a cutaneous allergic disorder characterized by peripheral eosinophilia, mast cell activation and predominance of Th2 cells.[56] In patients with atopic dermatitis, Gal 9 immunoreactivity is detected in epidermal keratinocytes and mast cells, which are also its main source in the lesional skin; the intensity of the expression is stronger, as compared to that in normal skin and is also evident in some infiltrating mast cells in the upper dermis.[56] Additionally, the levels of Gal 9 are elevated in the serum of patients with atopic dermatitis, as compared to healthy controls; these levescorrelate with the area of eczematous lesions and their severity index and decrease after treatment. These results indicate that Gal 9 may be used as a clinical marker of the severity of the disease and suggest that the Th2-polarized microenvironment in the lesional skin of patients with atopic dermatitis induces a Gal 9 upregulation and consequently exacerbation of Th2 polarization through accumulation of mast cells, after possible interaction of the latter with the epidermal keratinocytes.[56] In view of these effects, it seems reasonable to assume that Gal 9 may represent a novel therapeutic target in the management of atopic dermatitis.

Systemic scleroderma

It is well known that in patients with systemic scleroderma dermal fibroblasts promote skin-localized transdifferentiation of regulatory T cells to T helper (Th) type 2-like cells. Nevertheless, the exact mechanisms underlying the interaction of dermal fibroblasts with immune cells in this disease remain to be elucidated. In view of the capability of Gal 9 to induce Th2 cytokine-predominant immune imbalance by negative regulation of Th1/Th17 cells, Saigusa et al.[57] investigated the contribution of Gal 9 to Th immune balance in the lesional skin of patients with systemic scleroderma and found that this galectin was overexpressed in the dermal fibroblasts of the patients in vivo and in vitro, whereas serum Gal 9 levels were significantly elevated and positively correlated with skin score. These authors provided evidence suggesting that dermal fibroblasts derived from patients with systemic scleroderma suppress interferon-γ expression of skin-infiltrating $CD4^+$ T cells through Gal 9 overproduction and promote skin fibrosis.[55] The question as to whether administration of Gal 9 inhibitors/antagonists may be a novel approach to the treatment of systemic scleroderma remains to be elucidated in future studies.

CUTANEOUS NEOPLASMS

Epithelial

Apart from the study of Cada et al.[27], who observed a weak to moderate Gal 9 immunoreactivity in basal cell carcinomas, all available data on the expression of this galectin in epithelial neoplasms originate from studies on SCCs of the head and neck region and are conflicting. In contrast to the normal mucosa that revealed Gal 9 expression in the epithelial cells of the basal layer, all tested oral SCCs were completely devoid of any immunoreactivity for Gal 9 in the epithelial tumor cells.[58] This finding was interpreted by the authors as a result of microenvironment alterations occurring during the process of tissue dysplasia up to malignant transformation.

On the contrary, Muniz et al.[59] found increased immunoreactivity for Gal 9 in oral SCCs, as compared to normal mucosa and leukoplakia and suggested that the significant expression of Gal 9 in these tumors may be helpful for their differentiation from other oral cavity lesions.

Melanomas

Gal 9 expression is downregulated in primary melanomas, as compared to melanocytic nevi, whereas metastatic melanomas exhibit minimal or no immunoreactivity for this galectin.[60]. In primary melanomas, immunoreactivity is mostly detected in the cytoplasm of melanoma cells and in some cases also in the nucleus. In addition, most melanoma cells exhibiting nest formation reveal an increased cytoplasmic expression, as compared to those with little or without nest formation, thus, suggesting that Gal 9 may play a significant role in the mechanisms underlying the nest formation of melanocytic cells.[60]

Since patients with melanoma demonstrating high Gal 9 expression show significantly lower rates of lymph node metastasis, recurrence and death than those with low expression of this galectin, Kageshita et al.[60] put forth the hypothesis that high Gal 9 expression in primary melanomas is associated with a better prognosis. Interestingly, in experimental studies it has been shown that Gal 9 suppresses melanoma metastasis by blocking the adhesion of malignant cells to endothelium and extracellular matrices, whereas loss of its expression is closely associated with metastatic progression of melanoma.[61]

Human recombinant Gal 9 [Gal 9 (0)] is resistant to proteolysis, since it is devoid of the peptide that links its two CRDs. Gal 9(0) was found to exert distinct and previously unrecognized cytotoxic effects on melanoma cells in vitro by causing their rapid apoptotic death.[62] Based on this finding, it has been suggested that Gal 9(0) may represent a novel therapeutic agent for the management of human metastatic melanoma.[62]

In view of the negative regulation of Th1 immune response by Gal 9, which promotes Th2 type immunity favoring tumor development[63], Enninga et al.[64] studied the effects of this galectin on the immune response of patients with metastatic melanoma. They found a high expression of Gal 9 at the melanoma tumor edge and a significant (3.6-fold) increase in the plasma Gal 9 levels of patients, as compared to healthy controls. Interestingly, the latter finding was associated with systemic Th2 polarization and worse survival rate (independent from clinical factors), as compared to that of patients with a low or no increase in Gal 9 plasma levels. These findings suggest that plasma levels of Gal 9 may be regarded as a prognostic marker in metastatic melanoma and that this galectin may represent a novel therapeutic target of immunotherapy in order to achieve a recovery of Th1 tumor targeting immune state[64].

In view of these discrepancies and the complexity of Gal 9 biological actions, it is clear that further studies are now warranted in order to a. define the role played by the immunomodulatory, antiadhesive and pro-apoptotic effects of Gal 9 in the mechanisms of melanoma growth and metastasis and b. accurately assess the therapeutic potential of this galectin or its inhibitors in the management of melanoma.

HIV-INFECTION

Gal 9 is known to cause a reduction of Th1 and Th17 cells and an increase of anti-inflammatory regulatory T cells. In chronic HIV-1 infection, plasma levels of this galectin were found to correlate with HIV-1 viral load.[65] In patients with acute HIV infection plasma levels of Gal 9 were extremely elevated (50-fold) but revealed a rapid and marked decrease after treatment.[66] This rapid decline may be associated with clinical amelioration, since Gal 9 interacts with Tim-3 expressed on the surface of activated CD4(+) T cells and reduces their susceptibility to HIV-1 infection and replication.[65] Based on this finding, the authors suggested that plasma levels of Gal 9 may predict a severe inflammation status during the acute phase of HIV-1 infection and represent a potential biomarker of this disorder during its acute phase.

Abdel-Mohsen et al.[67] found out that administration of recombinant Gal 9 reverses HIV latency in both, an experimental model in vitro and in primary CD4+ T cells ex vivo obtained from HIV-infected, through antiretroviral therapy (ART) immunosuppressed individuals. These authors suggested that Gal 9 is capable of regulating HIV transcription and viral production *in vivo* during therapy and that Gal 9 manipulation through modulation of endogenous production or exogenous administration of the recombinant protein may significantly contribute to the development of novel therapeutic or even curative approaches to HIV infection.

CONCLUSIONS

Galectins are small and highly conserved proteins that are widely distributed in nature, bind to a variety of glycoproteins and glycolipids bearing β-galactoside residues and interact with diverse non-glycosylated molecules within the nucleus and the cytoplasm.

Galectins 7 and 9, representatives of the prototypical and tandem-repeat type of galectins, respectively, are involved in diverse fundamental molecular and cellular processes occurring in cutaneous and extracutaneous tissues including proliferation, apoptosis, differentiation, immune and inflammatory response, tumor cell growth, migration, invasion, and metastasis.

Disturbances in the distribution and expression of Gal 7 and Gal 9 found in a variety of cutaneous disorders may be involved in their pathogenesis. Accumulating experimental and clinical evidence strongly suggests that the administration of these galectins or their inhibitors/antagonists may open up entirely new avenues in the treatment of various cutaneous disorders (e.g. lymphomas, lichen amyloidosus, wounds, psoriasis, atopic dermatitis, systemic scleroderma, melanoma and HIV-infection). Further data may provide a more thorough understanding of the mechanisms involved in the pathogenesis of several cutaneous diseases, as well as the processes underlying the biological function of Gal 7 and Gal 9.

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