Galectin 3: an extraordinary multifunctional protein in dermatology. Current knowledge and perspectives*

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Abstract: Galectin 3 is a unique ~31 kDa protein that recognizes the N-acetyl-lactosamine structure of several glycoconjugates. It mainly occurs in epithelial and myeloid cells, but is also found in a variety of human cell types. In view of the crucial role played by galectin 3 in the regulation of cellular processes of essential importance and in the pathogenetic mechanisms of diverse disorders, it is not surprising that, particularly in the last three decades, the attention of the scientific community has been increasingly drawn to this extraordinary and multifunctional galectin. In this paper the authors summarize current knowledge on the expression of galectin 3 in normal and diseased human skin, its implications in the pathogenesis, diagnosis and prognosis of cutaneous disorders, and the perspectives of a novel approach to the treatment of the latter using galectin 3 or its inhibitors/antagonists.

Keywords: Carbohydrates; Epidermis; Galectin 3; Galectins

INTRODUCTION

Galectins constitute a family of small and highly conserved soluble proteins that occur in human cells and tissues and in diverse mammals, fungi, nematodes, sponges, insects, and viruses. They reveal a high binding affinity for β-galactose in glycoconjugates, which varies depending on the structure of the latter and the modifications of their galactose residues, such as sialylation, fucosylation, and sulfation.¹² Among the 17 mammalian galectins identified so far, 12 occur in humans.

Recent accumulating evidence suggests that 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.³

The purpose of study paper is to summarize current knowledge on the expression of galectin 3 (Gal 3) in normal and diseased human skin and on its potential functions and implications in the pathogenesis, diagnosis, prognosis, and treatment of cutaneous disorders. The overview of the available data is based on the results of an thorough electronic literature research that was conducted on the MEDLINE and SCOPUS databases through April 2018 using various combinations of the primary keyword “Galectins” with relevant terms.

GALECTIN 3

Gal 3 is a unique ~31 kDa protein that recognizes the N-acetyl-lactosamine structure of several glycoconjugates; in humans it is encoded by LGALS3 gene that is located on chromosome 14 (locus q21–q22). Gal 3 is widely distributed throughout the body, mainly occurs in epithelial and myeloid cells, but is also found in a variety of cell types in the skin and extracutaneous tissues.¹ It is secreted by activated macrophages and T- and B-cells, monocytes, Langerhans cells, dendritic cells, neutrophils, basophils, eosinophils, NK cells,
Gal 3 is mainly located in the cytoplasm where it is synthesized on free ribosomes, but also occurs in the nucleus, the cell surface and in the extracellular space and is secreted from cells by ectocytosis, a new non-classical secretory pathway. Gal 3 reveals a large spectrum of biological functions in normal and pathophysiological conditions and regulates diverse fundamental processes at the molecular and cellular level.\(^6\)-\(^8\),\(^10\) (Chart 1).

**NORMAL HUMAN SKIN**

In the adult normal human epidermis Gal 3 is found in the cytoplasm of normal keratinocytes with perinuclear enhancement\(^1\),\(^11\),\(^12\) in both the basal and the suprabasal layers; in the latter Gal 3 is co-localized with desmosomal proteins.\(^13\)-\(^17\) In keratinocyte cultures Gal 3 is upregulated upon enhancement of differentiation.\(^18\) These findings, taken together with the ability of Gal 3 to bind to laminin and enhance keratinocyte motility, suggest that the expression of this galectin may be related to the differentiation and maturation of keratinocytes.\(^19\)

The results of studies on the expression of Gal 3 in normal human melanocytes are conflicting. Mollenhauer \textit{et al.}\(^16\) failed to detect any Gal 3 immunoreactivity in melanocytes, whereas Chalupa \textit{et al.}\(^20\) detected Gal 3 predominantly in the melanocytic cell body peripherally along the Golgi zone co-localized with melanosome-des- tined cargo, specifically tyrosinase and tyrosinase-related protein-1 (tyr-1). Since downregulation of Gal 3 in human melanocytes resulted in reduction of both melanin synthesis and expression/activity of tyr-1, these authors suggested that Gal 3 may represent a regulatory factor of melanin synthesis affecting the expression of tyr-1.

In normal human skin, Gal 3 produced and released by the epidermal keratinocytes binds to the surface of Langerhans cells and is then internalized into the Birbeck granules, which participate in the process of antigen presentation.\(^1\),\(^2\) The expression of Gal 3 on the surface of dendritic cells positively correlates with the degree of their maturation\(^22\) and may be related to their migratory potential.\(^23\) Indeed, Gal 3/−/− bone marrow-derived dendritic cells reveal an impaired migratory response to chemokines \textit{in vitro} and a reduced migration to lymph nodes \textit{in vivo}, as compared to the gal Gal 3+/+ ones.\(^19\)

In mast cells, Gal 3 expression is found in the cytoplasm (over secretory granules) and the nucleus (heterochromatin). The immunoreactivity for this lectin in cutaneous mast cells is more intense, as compared to that of basophils and mast cells localized in other tissues. Gal 3 is released by these cell types when they are activated and degranulate, a finding that supports a possible role of this galectin in molecular and cellular events associated with mast cells and basophils, particularly in immediate type hypersensitivity reactions.\(^24\) Moreover, since Gal 3 is a major non-integrin laminin-binding protein, it seems reasonable to suggest that it may be involved in mechanisms underlying the promotion of mast cell adhesion to the basement membranes.\(^25\) In macrophages, which are the major source of Gal 3, this galectin is overexpressed\(^26\) and contributes to FcγR-mediated phagocytosis of erythrocytes, whereas extracellular Gal 3 is known to augment phagocytosis of apoptotic neutrophils by macrophages.\(^27\),\(^28\)

Gal 3 immunoreactivity is also found in the sweat glands and the sebaceous glands, whereas in human hair follicles it is located in the cells of the inner root sheath.\(^16\)

**CUTANEOUS DISORDERS**

**Psoriasis**

Gal 3 expression is lower in the keratinocytes of psoriatic epidermis, as compared to normal epidermis, but it is strong in the Langerhans cells of the psoriatic lesions.\(^2\) Interestingly, this galectin is also strongly expressed in the dermal capillaries of psoriatic lesions, indicating that both Gal 3 and its glycoligands may be involved in dermal capillary rearrangement and inflammatory cell recruitment.\(^13\),\(^30\) The latter finding could be interpreted in terms of Gal 3 induced alterations in the dermal capillary network structure and function in the psoriatic lesions. This hypothesis is also supported by the observation that Gal 3 enhances the formation of capillaries under \textit{in vitro} conditions.\(^11\),\(^19\)

Recently, Shi \textit{et al.} reported that Gal 3 expression is significantly downregulated in lesional epidermis, but not in the epidermis of the apparently normal skin of psoriatic patients, or in the lesional epidermis of patients with psoriasisform dermatitis, and it became detectable again in the regressive psoriatic lesions.\(^3\) Furthermore, these authors observed that the deficiency of epidermal Gal 3 was capable of inducing psoriasisform lesions in the skin of Gal 3/−/− mice subsequent to topical imiquimod application and in the skin of these mice after its transplantation onto wildtype mice. These lesions were found to be caused by the spontaneous triggering of psoriatic profile of the keratinocytes through the JNK pathway and the accumulation of neutrophils due to the increased leukocyte recruiting capacity of Gal 3 deficient keratinocytes. Indeed, recombiant Gal 3 was found to suppress \textit{in vitro} the production of inflammatory molecules such as S100A8/9, CXLI, and CCL20 by the Gal 3 deficient keratinocytes.

The most important finding of this study was the impressive improvement of imiquimod-induced psoriasisform dermatitis in Gal 3/−/− mice subsequent to restoration of Gal 3 levels in the skin by intracutaneous injection of recombiant human Gal 3. The exciting results of the study of Shi \textit{et al.} suggest that Gal 3 deficiency

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**Chart 1. Most significant biological actions of galectin 3 in human tissues**

| Inhibition of apoptosis |
|------------------------|
| Regulation of extracellular matrix and epithelial cell interactions |
| Modulation of cell migration and adhesion |
| Involvement in the mechanisms of cell activation and chemotraction |
| Significant regulatory role in cell growth and differentiation |
| Regulation of plasma membrane organization |
| Regulation of signal transduction |
| Regulation of immune surveillance |
| Promotion of angiogenesis \textit{in vivo} and \textit{in vitro} |
| Proinflammatory activity through macrophage activation and migration |
| Direct binding to pathogens |
| Induction of fibrosis through increase in fibroblast proliferation and collagen production |
may be used as a novel and distinctive diagnostic marker of psoriasis and that administration of recombinant Gal 3 may represent a new and promising approach to the treatment of this keratinization disorder.\textsuperscript{31}

Interestingly, an unexpected observation, that is inconsistent with the experimental findings of Shi \textit{et al.} and the established gal 3 deficiency in psoriasis, was made during phase 2 clinical studies on the efficacy of a Gal 3 inhibitor (GR-MD-02) in the management of nonalcoholic steatohepatitis: a female patient with coexisting plaque psoriasis which was treated with this compound showed a complete remission of her skin lesions (ClinicalTrials.gov Identifier: NCT01899859).\textsuperscript{31}

Based on this observation, Ritchie \textit{et al.} studied the therapeutic efficacy and safety of GR-MD-02 in five adult patients with moderate to severe plaque psoriasis.\textsuperscript{32} Subsequent to a six-month continuous monotherapy with intravenous infusions of this inhibitor (at a dose of 8 mg/kg every other week), an average 51.9% reduction of Psoriasis Area and Severity Index (PASI) was seen in the treated patients. One of them revealed a slight rise of PASI score during the six-month follow-up; however, he still revealed a 25% reduction of pretreatment PASI score. The therapeutic results of GR-MD-02 found in this first clinical trial are rather moderate, as compared to those of other regimens; however, taken together with the absence of any serious adverse drug reactions, they indicate that subsequent to the identification of the optimal therapeutic dose of GR-MD-02 in dose-finding studies, randomized controlled clinical trials on large numbers of psoriatic patients are warranted in order to exactly define the therapeutic efficacy and safety of this Gal 3 inhibitor in the management of chronic plaque psoriasis.

**Neoplasms**

**Epithelial**

The results of studies performed on the expression of Gal 3 in epithelial cutaneous neoplasms are conflicting. Upregulation of this galectin was reported in head and neck squamous cell carcinomas (SCCs) and in oral carcinomas\textsuperscript{33} whereas in the most common cutaneous epithelial neoplasms basal cell carcinomas (BCCs) and SCCs Gal 3 expression is clearly reduced or absent.\textsuperscript{34}

In circumscribed and infiltrative BCCs, cytoplasmic Gal 3 immunoreactivity was significantly more pronounced than the nuclear immunoreactivity. Moreover, no correlation was detected between BCC tumor size and Gal 3 immunoreactivity.\textsuperscript{35} Since it is unclear whether BCCs originate from basal cells, from the outer root sheaths of the hair follicles, or from both structures, Mollenhauer \textit{et al.} pointed out that Gal 3 absence in BCCs indicates an important role played by Gal 3 inactivation in the pathogenesis of BCCs.\textsuperscript{36}

The findings of comparative studies on Gal 3 expression in normal human epidermis and SCCs are inconsistent. Kapucuoglu \textit{et al.}\textsuperscript{37} found no differences, whereas Mollenhauer \textit{et al.}\textsuperscript{38} reported a substantial reduction of Gal 3 levels in SCCs. Interestingly, Kapucuoglu \textit{et al.} found a significantly higher cytoplasmic immunoreactivity in SCCs, as compared to BCCs, and suggested that this finding may indicate a different biological behavior of these two tumors.\textsuperscript{39} In SCCs, a positive correlation between the intensity of cytoplasmic Gal 3 expression and the tumor size was reported, a finding that is regarded by the authors as indication that Gal 3 may contribute to the mechanisms of tumor enlargement through its anti-apoptotic activity.

Jiang \textit{et al.} reported that in both benign skin disorders with epidermal hyperplasia and epithelial skin cancers (BCCs and SCCs) there was a significant downregulation of Gal 3 immunoreactivity, which, however, was comparable among the benign disorders and the neoplasms.\textsuperscript{40} They suggested, therefore, that this finding points toward a regulatory pathway independent of the differentiation status of epidermal keratinocytes. Interestingly, since a downregulation of both, Gal 3 and DMBT-1 (protein with mucin-like structure critical for carcinogenesis) is detected in most cutaneous epithelial neoplasms, it has been hypothesized that the interactions of these factors may be implicated in the pathogenetic mechanisms of these tumors.\textsuperscript{41,42}

Keratoacanthomas showed staining pattern similar to that seen in SCCs with the least differentiated outer cell layers being invariably negative.\textsuperscript{43} Jiang \textit{et al.} reported that in keratoacanthomas slightly positive signals for Gal 3 were mainly localized in well-differentiated and well-arranged keratinocytes in lobular structures, whereas no signals were observed in cells with a glassy appearance in deeper areas.\textsuperscript{44}

**Melanomas**

Absent or minimal expression (predominantly cytoplasmic) of Gal 3 has been reported in the melanocytes in benign melanocytic nevi in both junctional and dermal compartments\textsuperscript{45} and in the intraepidermal component of dysplastic nevi with increasing Gal 3 expression as the lesions progress from dysplastic nevi to melanomas.\textsuperscript{46} Gal 3 expression is stronger in thin primary melanomas, as compared to benign nevi, but is progressively reduced during the development of thick and metastatic melanomas.\textsuperscript{47,48} Prieto \textit{et al.} reported that in metastatic melanomas there was an increase in both, the levels of Gal 3 and the nuclear/cytoplasmic ratio of Gal 3 expression, as compared to primary melanomas and that nuclear Gal 3 expression correlated well with the prognosis of this tumor.\textsuperscript{49}

In melanoma cells Gal 3 expression is mainly localized in the cytoplasm and in some cases also on the cell membranes and nucleus.\textsuperscript{50,51} It has been suggested that Gal 3 overexpression in primary cutaneous melanomas may reflect a more aggressive local behavior and metastasizing phenotype; thus Gal 3 may be capable of playing a significant role in the development, progression and prognosis of melanoma.\textsuperscript{52} Additionally, metalloproteinases released by melanoma cells may use Gal 3 as a substrate.\textsuperscript{39,43} Brown \textit{et al.} suggested that melanoma progression is associated with a depletion of intracellular Gal 3 stores and as a consequence, the decrease in Gal 3 expression may be associated with an increased risk of metastasis and a worse overall prognosis in primary melanoma.\textsuperscript{53}

Using a xenograft melanoma model with human melanoma cell lines, Vereeken \textit{et al.} found that in advanced lesions Gal 3 expression was decreased and inversely correlated with aggressiveness, possibly serving as a trigger of intense proliferation.\textsuperscript{44} Serum Gal 3 concentrations are increased in patients with melanoma, probably due to increased production either by inflammatory cells or by the melanoma cells and are related to serum levels of other pa-
rameters of inflammation and Gal 3 immunoreactivity in cutaneous metastases.\textsuperscript{44, 45}

Li et al. reported that nuclear expression of Gal 3 was higher in primary cutaneous melanomas than in primary mucosal melanomas or in melanomas with metastases.\textsuperscript{46} Moreover, since it correlat-
ed with necrosis and the age and survival time of patients, these authors suggested that the decrease in nuclear expression of Gal 3 may represent a poor prognostic factor for melanomas.

Pozca et al. reported that elastin-derived peptides generated subsequently to elastin degradation by matrix metalloproteinases increase the invasive potential of melanoma cells and that this effect is predominantly mediated by the cell surface gal 3 receptor.\textsuperscript{47} They suggested, therefore, that a more selective and effective treatment of melanoma could be achieved by inhibition of migration and invasion of melanoma cells using antagonists of gal 3 receptor.

Adoptive T-cell transfer with \textit{ex vivo} expanded tumor-reactive T-cells generated in mixed lymphocyte melanoma cell cultures is effective in the management of metastatic melanoma.\textsuperscript{48} Gal 3 and indoleamine 2,3-dioxygenase (IDO), both produced by the melanoma cells, as well as the accumulation of CD4\textsuperscript{+}CD25\textsuperscript{+}FoxP3 T cells suppress the expansion of melanoma-reactive T cells; on the contrary, elimination of melanoma-derived Gal 3 and IDO improve the latter.\textsuperscript{49} These observations may open the way for new and promising approaches to the treatment of metastatic melanoma using Gal 3 inhibitors.

\textbf{Cutaneous T-cell lymphomas}

Recently, Thode \textit{et al.} using an organotypic model of cutaneous T-cell lymphoma (CTCL) showed that malignant T-cells markedly stimulate the growth of keratinocytes through secretion of galectins 1 and 3 and cause disorganization of keratinocyte stratifica-
tion that resembles the early hyperproliferative phase of cutaneous lesions in CTCL.\textsuperscript{50}

Mittendorf \textit{et al.} comparatively investigated the expression of Gal 3 in the skin lesions of patients with primary cutaneous anaplastic large-cell lymphomas (PCALCL), lymphomatoid papulosis (LVP), and transformed mycosis fungoides with CD30 expression (MF-T).\textsuperscript{51} They found a significantly reduced expression of this galectin in the CD30\textsuperscript{+} tumor cells of MF-T, as compared to that in CD30\textsuperscript{+} lymphoproliferative disorders (CD30 LPD), but detected no differences between PCALCL and LVP. In PCALCL Gal 3 was more often localized in the cytoplasm in contrast to LYP, in which an equal distribution in the cytoplasm and the nucleus was more common. These authors suggested that the downregulation of Gal 3 expression in MF-T (in comparison to CD30 LPD) might be used as an additional criterion to differentiate both entities, whereas the different sublocalization of the Gal 3 signal might reflect a different biological function and behavior.

\textbf{Miscellaneous}

\textbf{Wounds}

EGF-mediated EGFR-ERK signaling is of outmost importance for keratinocyte migration, a decisive prerequisite for re-epi-
thelialization of skin wounds.\textsuperscript{52} Liu \textit{et al.}, using cells isolated from gal 3 deficient mice, demonstrated that in the absence of Gal 3, both keratinocyte migration and skin wound re-epithelialization are im-
paired.\textsuperscript{53} These authors concluded that the pro-migratory effects of Gal 3 are exerted through regulation of EGFR intracellular trafficking, being carbohydrate independent.

It is known that Gal 3 serves as a receptor for advanced glycation end products (AGEs) leading to their binding and clear-
ance. AGEs are thought to contribute to the defective skin repair in diabetic patients. Using immunohistochemistry, Pepe \textit{et al.} studied the expression of Gal 3 in tissue derived from chronic wounds and apparently normal skin from the same patient, and found that Gal 3 was strongly expressed in the epidermis and the vasculature of the apparently normal skin and greatly reduced at the wound edge and in the wound bed, in which AGEs labeling was increased.\textsuperscript{54} Based on this inverse correlation between Gal 3 and AGEs, the authors suggested that Gal 3 may protect against AGEs accumulation in wound healing.\textsuperscript{55}

In view of Gal 3’s implications in cutaneous wound healing, McLeod \textit{et al.} investigated the efficacy of human recombinant Gal 3 in the treatment of wounds in wild type and diabetic mice.\textsuperscript{56} He found that \textit{in vivo} topical application of either Gal 3 or gelatin/ gal 3 scaffolds did not affect wound closure, epithelial thickness, re-epithelialization, or macrophage phenotypes in the wound.

\textbf{Allergic contact and atopic dermatitis}

Gal 3 plays a significant role in the pathogenesis of cutaneous inflammation, since it induces macrophage, lymphoid, and myeloid cell activation,\textsuperscript{57} increases cell adhesion of myeloid cells,\textsuperscript{58} promotes chemotraction of monocytes and macrophages,\textsuperscript{59} and regulates the response and function of diverse immune cell popu-
lations.\textsuperscript{60}

Recently, Navarro-Alvarez \textit{et al.} reported that Gal 3 plasma depletion apheresis in a cutaneous inflammation porcine model through binding immuno-affinity is capable of causing a significant decrease in skin inflammation. Since this method can be also successfully used in human subjects, these authors suggested that it may represent a novel approach to the treatment of cutaneous inflammatory disorders.\textsuperscript{61}

It is well known that keratinocytes of human epidermis serve as the primary target of nickel, a major contact allergen.\textsuperscript{62} Interestingly, it has been shown that epidermal exposure to nickel leads to the suppression of Gal 3 in epidermal keratinocytes.\textsuperscript{63} Moreover, intracellular Gal 3 was found to positively regulate allergic contact dermatitis in experimental animals,\textsuperscript{64} possibly through the effects of this galectin on Langerhans cells and other dendritic cells.

Saezuga \textit{et al.} reported that in patients with atopic dermatitis Gal 3 expression is upregulated in inflammatory cells in the les-
íonal skin but not in their apparently normal skin.\textsuperscript{65}

These authors studied the influence of intracellular Gal 3 on the development of allergic inflammatory response in a mouse model of the acute phase of atopic dermatitis subsequent to repeat-
ed epicutaneous sensitization with ovalbumin. They detected an upregulation of Gal 3 expression at sites with inflammation induced by the sensitization. In Gal 3 deficient mice the overall inflammatory response, the thickness of the epidermis, the density of eosinophilic and monocytes infiltrate, the serum ovalbumin-specific IgE concen-
Galactoside recognition by galectins

Galactose is the main sugar moiety of glycoproteins and glycolipids, and it is also present in the bacterial endotoxins of Gram-negative bacteria. The molecular structure of galectins is unique among the serpins, and their recognition of the galactose moiety is mediated by a carbohydrate recognition domain (CRD) that is composed of several α-helical and β-sandwich structures.

The galectin family includes 15 members that are ubiquitously expressed in tissues and cell types, and they are characterized by their ability to bind to glycoproteins and glycolipids that contain the β-galactoside and α-mannose residues of a common β-galactose unit.

The Gal-3 molecule is a member of the galectin family, and it is widely expressed in various tissues and cell types, including epithelial, dermal, endothelial, and hematopoietic cells. The Gal-3 protein is a multifunctional molecule that plays a crucial role in the pathogenesis and progression of several chronic inflammatory, autoimmune, and neoplastic diseases.

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Behcet’s disease

Serum Gal-3 total levels were found to be significantly higher in Behcet’s disease (BD) patients, when compared to healthy controls. Interestingly, patients with active BD revealed significantly higher serum Gal-3 levels, as compared to inactive patients and controls and higher Gal-3-binding protein (G3BP) serum levels than the controls. Additionally, serum levels of both Gal-3 and G3BP positively correlated with the BD severity score.64,65 These results suggest that serum Gal-3 and G3BP levels may represent new biomarkers indicating the degree of BD clinical activity. It should be noted, however, that their rise in the active phase is not specific for BD, since it is also evident in patients with leukocytoclastic vasculitis.

Systemic sclerosis

In view of the involvement of Gal-3 in the pathogenetic mechanisms of fibrosis,66 serum concentrations of this galectin have been determined in patients with systemic sclerosis and were found to be markedly increased, as compared to healthy controls and correlating with the extent of cutaneous fibrosis.67,68 Recently, Faludi et al. reported that in patients with systemic sclerosis Gal-3 is an independent and reliable biomarker to predict all-cause and cardiovascular-related mortality, and that the serum levels of this galectin are clearly associated with advanced organ fibrosis and inflammation.69

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. Gal-3 is a unique ~31 kDa protein that recognizes the N-acetyl-lactosamine structure of several glycoconjugates. Gal-3 regulates diverse fundamental molecular and cellular processes including proliferation, apoptosis, differentiation, immune and inflammatory response, tumor cell growth, migration, invasion, and metastasis.

In normal adult human skin Gal-3 is expressed in the cytoplasm of keratinocytes in the basal and particularly in the suprabasal layers, in hair follicles, sweat and sebaceous glands, in the extracellular matrix of the dermis, in proliferating fibroblasts, Langhans cells, mast cells, and melanocytes.

Disturbances in the distribution and expression of Gal-3 are associated with a variety of cutaneous disorders in the pathogenetic mechanisms of which this galectin may be involved.

Accumulating experimental and clinical evidence strongly suggests that the introduction and clinical use of inhibitors/antagonists of Gal-3 may open up entirely new avenues in the treatment of cutaneous inflammatory and neoplastic disorders (psoriasis, atopic dermatitis, and melanoma), and may provide a more thorough understanding of and a deep insight into both the mechanisms of their pathogenesis and the processes underlying the biological function of Gal-3.
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