

# Lipocalin 2 Participates in the Epidermal Differentiation and Inflammatory Processes of Psoriasis

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**Abstract:** As a multifunctional cytokine, lipocalin 2 is weakly expressed in skin and serum under normal conditions. However, it is over-expressed by neutrophils and keratinocytes in the skin lesions and sera in several skin diseases. Recent studies demonstrated that lipocalin 2 participates in the pathogenesis of psoriasis by exerting versatile effects on skin resident cells and infiltrating immune cells. Lipocalin 2 inhibits the synthesis of keratin, involucrin, and loricrin in keratinocytes, leading to epidermal parakeratosis via the Tcf711-lipocalin 2 signaling axis. It also recruits inflammatory cells such as T cells and neutrophils into skin lesions via the IL-23/IL17, p38-MAPK, and ERK-1/2 signaling pathways. Additionally, lipocalin 2 and other cytokines such as IL-17 have the synergetic effects on skin cells. The neutralization of lipocalin 2 or relevant cytokines can alleviate psoriasis, verifying that lipocalin 2 is an effective interfering target for psoriasis. In this review, we summarize the roles of lipocalin 2 in the processes of psoriatic inflammation and the promising therapeutic strategies based on lipocalin 2-related molecules.

**Keywords:** lipocalin 2, psoriasis, keratinocyte, inflammation, differentiation

## Introduction

Psoriasis is a common, chronic, immune-mediated dermatosis affected by genetic and environmental factors that can be triggered by injuries, infections, or mechanical stimulation.<sup>1</sup> The fundamental mechanism of psoriasis consists of three main aspects: immune and inflammatory cell infiltration, vascular proliferation and skin hyperplasia,<sup>2</sup> and abnormal differentiation of keratinocytes.<sup>3,4</sup> In terms of immune mediation, activated CD4<sup>+</sup>, CD8<sup>+</sup> T lymphocytes, CD3 T cells, macrophages, mast cells,<sup>5</sup> keratinocytes, dendritic cells, and neutrophils lead to innate and adaptive immune responses by the release of cytokines and enzymes in psoriasis.<sup>6-8</sup> During the inflammation process, interleukin (IL)-23 and IL-12, secreted by dendritic cells, activate Th1 and Th17 cells to produce cytokines such as IL-17, interferon (IFN)- $\gamma$ , and tumor necrosis factor (TNF)- $\alpha$ . This leads to macrophage migration, keratinocyte proliferation,<sup>9</sup> and neovascularization, subsequently resulting in the appearance of psoriatic scaly plaques.

Lipocalin 2 is a 25-kDa glycoprotein coded in a gene located at chromosome 9q34.11, and it is composed of an N-linked low-molecular weight polysaccharide and a protein backbone. With this kind of structure, lipocalin 2 can bind with three receptors including megalin,<sup>10</sup> 24p3R, and melanocortin-4. It possesses a lipophilic barrel-shaped tertiary structure and binds with matrix metalloproteinase (MMP)-9 in neutrophils for the inhibition of proteolysis of MMP-9.<sup>11,12</sup> In addition to secretion by granulocytes, lipocalin 2 is mainly secreted by a variety of cells, including keratinocytes,<sup>13</sup> adipocytes,<sup>14</sup> CD4<sup>+</sup> T cells,<sup>15</sup> macrophages,<sup>16</sup> and dendritic cells.<sup>17</sup> It is also produced in different tissues such as the liver, lungs, and kidneys.<sup>18</sup> Lipocalin 2 is widely expressed, although it was initially considered as an antimicrobial peptide that was increased in the plasma and tissues of patients with infectious diseases. In recent years, studies have shown that lipocalin 2 levels are also elevated in several inflammatory skin diseases such as psoriasis,<sup>19,20</sup> eczema, and skin wounds,<sup>21</sup> and its overexpression has even been detected in neoplasms for its potential role in cell proliferation in diseases such as keratoacanthoma and squamous cell

carcinoma.<sup>22,23</sup> Thus, lipocalin 2 functions in a versatile manner in antibiosis, inflammation, and cell differentiation or dysfunction.

Several studies have shown that lipocalin 2 levels are elevated in the skin lesions and serum of patients with psoriasis, and lipocalin 2 has been proved to be effective in regulating inflammation and cell proliferation in psoriasis.<sup>24</sup> There has been a large number of articles highlighting lipocalin 2's versatile functions, such as being an indicator for predicting the prognosis and mortality of neoplasms and psoriasis. However, there are few convincing pieces of evidence that highlight the diagnostic and treatment value of lipocalin 2. The relationship between lipocalin 2 and the onset or development of psoriasis remains unclear and should be elucidated. Here, we review the current findings regarding the effect of lipocalin 2 on the formation and development of psoriasis and suggest novel therapeutic strategies.

## Lipocalin 2 Functions in Both Innate and Adaptive Immune Responses

As the body's first line of defense, innate immunity plays a central role in antibacterial action.<sup>25</sup> Lipocalin 2 plays a non-negligible role in the innate immunity process not only by inducing the infiltration, migration, and adhesion of inflammatory cells such as neutrophils into skin lesions, but also by directly binding with iron-containing siderophores of bacteria to prevent their uptake of iron and limiting bacterial growth.<sup>26</sup> The depletion of lipocalin 2 in mice results in susceptibility to bacterial infection due to its function of maintaining microbiotic eubiosis and provoking inflammation.<sup>27,28</sup> IL-10 plays an important role in the anti-inflammatory response. *Lcn2* (coding lipocalin 2) deficiency can cause a significant decrease in IL-10 expression in cultured macrophages. The expression of IL-6, IL-1 $\beta$ , TNF- $\alpha$ , monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein 2, reactive oxygen species, and nitric oxide decreases in *Lcn2*-deficient mice.<sup>29</sup> Therefore, a lack of lipocalin 2 will impair the antibacterial effect of macrophages and neutrophils. In the antiviral response, lipocalin 2 inhibits the proliferation of T lymphocytes and exerts immune effects by regulating the antigen presentation activity of dendritic cells. Moreover, the expression of inflammatory cytokines such as IL-12, IFN- $\gamma$ , interferon-inducible protein (IP)-10, IL-6, MCP-1, B cell activating factor, and IFN- $\alpha$  increased, and in lipocalin 2-deficient mice with influenza, high mortality resulted.<sup>30</sup> Therefore, lipocalin 2 plays a significant role in balancing the proliferation of immune cells and the secretion of immune cytokines in the body's antiviral effect. Lipocalin 2 also modulates adaptive immunity either by contacting with T cells as a self-antigen or by interacting with the IL-23/IL-17 axis.<sup>31</sup> Obviously, the role of lipocalin 2 in innate and adaptive immune responses has not yet been clearly elucidated, and its interactions with various immune cells and inflammatory factors require further exploration.

## Lipocalin 2 Regulates Epidermal Differentiation

In addition to neutrophils, keratinocytes are the second main source of lipocalin 2. Evidence shows that lipocalin 2 participates in keratinocyte differentiation, and the appearance of overexpressed lipocalin 2 leads to skin disorders such as epidermal parakeratosis.<sup>22</sup> During skin development and cell differentiation in embryos, lipocalin 2 is initially weakly produced in the epidermis, then strongly expressed in granular and horny layers, and finally accumulates in the follicular epithelium. In contrast to lipocalin 2, filaggrin, as an indicator of cell differentiation, translocated from the perifollicular epithelium to the epidermis and was inhibited in psoriatic hyperplasia lesions where lipocalin 2 was overexpressed.<sup>32</sup> Thus, lipocalin 2 potentially inhibits the expression of filaggrin and induces dysfunction in the differentiation and proliferation of keratinocytes.

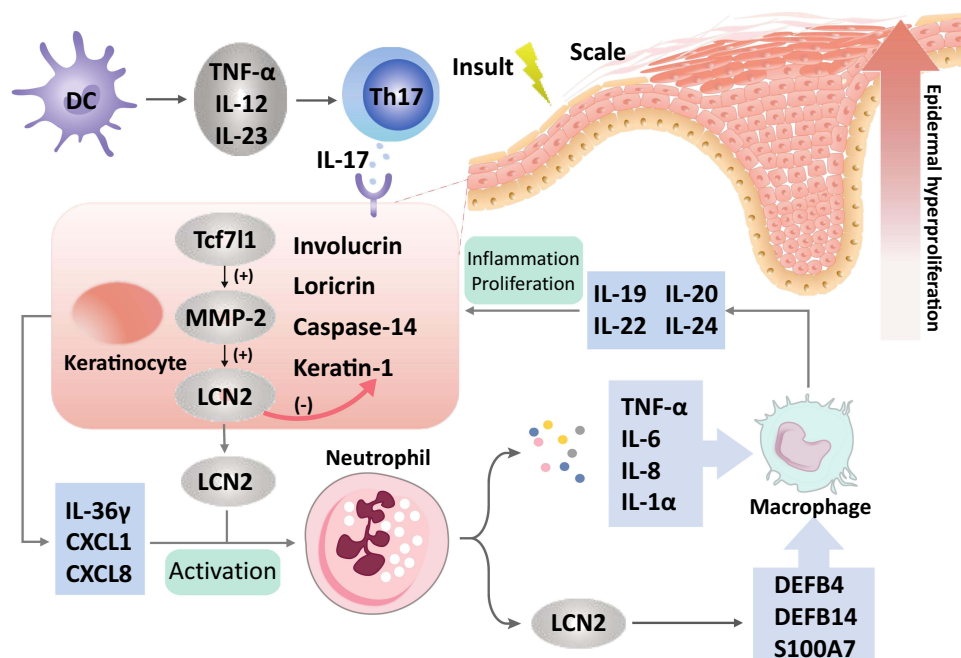
As a lipocalin 2 inducer that always predicts a poor differentiation condition of keratinocytes,<sup>33</sup> transcription factor 7-like 1 (Tcf7l1) facilitates the expression of lipocalin 2 in wounded skin repair by promoting the motility and differentiation of keratinocytes.<sup>21</sup> In vitro, human foreskin keratinocytes infected with papillomavirus and SCC-13 cells exhibited upregulated Tcf7l1 and lipocalin 2, with downregulated expression of involucrin and loricrin.<sup>34</sup> Moreover, inhibition of Tcf7l1 can eliminate the modulatory effect of lipocalin 2 on the keratinocyte differentiation process.<sup>35</sup> This result proves that Tcf7l1 and lipocalin 2 confer a synergistic effect on the modulation of keratinocyte proliferation. In addition, lipocalin 2 levels increased in squamous cell carcinoma and keratoacanthoma, whereas they decreased in basal cell carcinoma, which indicates that lipocalin 2 contributes to cell terminal differentiation and keratin synthesis.<sup>22</sup> Furthermore, lipocalin 2 dysregulates cell differentiation into a more immature phenotype by inhibiting the

nuclear factor  $\kappa$ B pathway,<sup>36</sup> upregulating p-Met, and phosphorylating p-focal adhesion kinase (FAK) to activate the Met/FAK cascade, and finally downregulating the epidermal marker E-cadherin while upregulating the mesenchymal marker.<sup>37</sup> Thus, these studies support the vital role of lipocalin 2 in regulating the differentiation and proliferation of keratinocytes.

## Lipocalin 2 Mediates the Psoriatic Inflammatory Responses

Several studies have elucidated the potential mechanisms of lipocalin 2 in the pathogenesis of psoriasis, which is related to the functions of manifold cells in a differential manner, as shown in Figure 1. One of them puts forward that psoriasis, as an inflammatory skin disorder, is mediated by the IL-23/IL-17 pathway. Lipocalin 2 is considered to participate in the genesis of psoriasis by modulating neutrophil functions and augmenting the Th17 cell response.<sup>13,38</sup> It has been determined that lipocalin 2 is a chemoattractant of neutrophils, which are designated to be activated by lipocalin 2 via one of the receptors on it, 24p3R.<sup>39</sup> Thereafter, neutrophils produced IL-6, IL-8, TNF- $\alpha$ , and IL-1 $\alpha$  via the extracellular signal-regulated kinase (ERK)-1/2 and p38-mitogen-activated protein kinase (MAPK) signaling pathway.<sup>13</sup> Moreover, keratinocytes play an indispensable role in producing psoriatic cytokines such as IL-17A, IL-22 and TNF- $\alpha$ , which enhance the formation and progression of psoriasis.<sup>13</sup> Produced by CD4<sup>+</sup> T cells and strongly associated with inflammation, IL-17 is transcriptionally stimulated by lipocalin 2,<sup>40</sup> stimulates the expression and secretion of lipocalin 2, and both of them have the synergetic effect of activating Th17 cells, which thus leads to the accumulation and activation of macrophages.<sup>41,42</sup> Additionally, injecting lipocalin 2 can stimulate dendritic cells to secrete IL-23p19, IL-12p40, and TNF- $\alpha$ . Neutralizing lipocalin 2 alleviates the hyperplasia of the psoriatic epidermis and decreases the expression of IL-17 and IL-23, which consequently decreases the infiltration of inflammatory cells into skin lesions. Moreover, lipocalin 2 also induced the secretion of multiple antimicrobial peptides or chemokines such as defensin beta (DEFB) 4, DEFB14, S100 calcium binding protein A7 (S100A7), and lipocalin 2 in imiquimod-induced psoriasis-like lesions accelerated the inflammatory process.<sup>38</sup>

In addition to inducing inflammation, previous research deduced that lipocalin 2 modulates cell differentiation and proliferation via the Tcf7l1-lipocalin 2 axis. Tcf7l1 is a pivotal protein that determines cell development and proliferation



**Figure 1** The effect of lipocalin 2 on skin-infiltrating cells and cytokines in psoriasis. Th17 cells produce IL-17, which regulates keratinocytes through the Tcf7l1-MMP-2-lipocalin 2 pathway and then activates neutrophils to secrete inflammatory cytokines such as TNF- $\alpha$ , IL-6, IL-8, IL-1 $\alpha$ , and lipocalin 2, which induce migration and accumulation of macrophages into psoriatic lesions. Lipocalin 2 also decreases the expression of involucrin, loricrin, caspase, and keratin-1, which aggravates the abnormal differentiation of keratinocytes. Meanwhile, keratinocytes secrete IL-36 $\gamma$ , lipocalin 2 (LCN2), CXCL1 and CXCL8 as a positive feedback loop to stimulate the inflammatory responses of neutrophils. These comprehensive effects thus lead to inflammation and hyperproliferation of the epidermis in psoriasis.

by regulating Wnt- $\beta$ -catenin and c-Myc signaling in different cells.<sup>43–45</sup> Tcf7l1 enhances the expression of MMP-2 from keratinocytes and then exerts its role in inducing lipocalin 2 upregulation in a circular feedback manner.<sup>34</sup> Hence, the Tcf7l1-lipocalin 2 axis is a potential pathogenesis pathway associated with the abnormal proliferation and differentiation of keratinocytes in psoriasis.

Approximately 30% of psoriasis patients are affected by psoriatic arthritis (PsA). In recent years, there has been some evidence that lipocalin 2 is correlated with PsA.<sup>13</sup> In PsA, neutrophils are indispensable for secreting lipocalin 2, which modulates Th17 cells secreting IL-17 and IL-22 and then leads to bone remodeling and the inflammation reaction.<sup>46–48</sup> In addition, the IL-23/IL-17 axis stimulates the expression of chemokine (C-X-C motif) ligand (CXCL) 1, CXCL2, CXCL5, and CXCL8/IL-8 in the PsA synovial membrane, contributing to neutrophil infiltration and recruitment,<sup>49,50</sup> as we have demonstrated in the pathogenesis of psoriasis. Hence, we deduced that lipocalin 2 also assumed an important role in the pathogenesis of PsA via the IL-23/IL-17 axis in order to induce inflammation and cell proliferation. Palmoplantar pustular psoriasis differs from psoriasis vulgaris in that it is derived from the eccrine gland.<sup>51</sup> Lipocalin 2, which is also expressed in sebaceous gland cells,<sup>52</sup> is thought to be induced by IL-1 $\beta$  in keratinocytes, which is indicated by serum lipocalin 2 levels that are positively related to the pustule score and Dermatology life quality index.<sup>39</sup> As a consequence, lipocalin 2 may act as an indicator of severity and prognosis in PsA and palmoplantar pustular psoriasis.

## Diagnostic and Therapeutic Strategies Based on Lipocalin 2 Signals

Psoriasis affects almost 1% of the worldwide population, and the diagnosis of psoriasis is primarily clinical, but the evaluation methods for prognosis require additional development.<sup>48</sup> In the past, serum c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels have been used to evaluate the treatment efficiency of psoriasis, but they have their own limitation of accuracy.<sup>53</sup> Recently, lipocalin 2 has been widely investigated as a promising biomarker for evaluating disease status or even a potential target for the treatment of psoriasis. For example, the serum lipocalin 2 level is positively related to IL-17, which is one of the targets for treating psoriasis, but measuring it with the current technology results in inaccuracy. Therefore, researchers proposed that serum lipocalin 2 is the best proxy of serum IL-17, and this may assist in guiding therapy and evaluating prognosis.<sup>53</sup> High levels of lipocalin 2 have been widely detected in skin, plasma, saliva, and other body fluids of patients and animals with psoriasis.<sup>13,39,54–56</sup> Some researchers reported that, in psoriasis patients, serum lipocalin 2 levels were significantly higher compared to those in healthy controls.<sup>18,57</sup> However, El-Hadidi et al did not show significant differences in lipocalin 2 sera levels compared to controls.<sup>58</sup> Except for serum, lipocalin 2 was diminished in psoriasis patients' saliva in contrast to healthy controls.<sup>59</sup> Moreover, in psoriatic skin lesions, lipocalin 2 has been widely detected highly expressed in the granular layer and hair follicles of psoriatic lesions compare to healthy controls.<sup>36,60–63</sup> In contrast to the level of lipocalin 2 in skin, the serum levels of lipocalin 2 in psoriasis patients are not always consistent with the high level in skin.<sup>18</sup> For example, a study concluded that there was no significant difference in patient serum lipocalin 2 levels after treatment.<sup>57</sup> These differences can be attributed to several factors. Firstly, lipocalin 2 is derived from manifold tissues, such as liver, lungs, and kidneys, adipocytes, macrophages, and epithelial cells. Moreover, the diversity of disease durations and severities, past medical history including complications and therapies, may also explain the contradictory results. Thus, lipocalin 2 may not fully reflect the severity degree of psoriasis.

Studies investigated the relationship between lipocalin 2 and the psoriasis area and severity index (PASI), pustule score, and dermatology life quality index, which are shown in Table 1.<sup>38,39,57,64,65</sup> We noticed that there are conflicting results regarding the correlation between lipocalin 2 and PASI score. Romani et al reported a positive correlation between baseline serum lipocalin 2 and PASI score.<sup>57</sup> Otherwise, in other studies, no correlation was found in several studies between serum or tissue lipocalin 2 and the disease duration, extent, treatment efficiency and PASI score.<sup>18,57,61,66</sup> Moreover, as an adipokine, lipocalin 2 has been investigated in psoriasis patients with atherosclerosis, metabolic syndrome, obesity, or diabetes mellitus.<sup>57,58,62</sup> While lipocalin 2 is an adipokine, researchers found no correlation between sera lipocalin 2 and Body Mass Index, lipid profile (high density lipoprotein-cholesterol (HDL-C), triglyceride and cholesterol) and a negative correlation between serum lipocalin 2, low density lipoprotein-cholesterol (LDL-C) and plasma glucose in psoriasis patients or controls.<sup>18</sup> Moreover, a study also reported no correlation between lipocalin 2 and BMI in patients with metabolic syndrome.<sup>63</sup> However, there still have different results reported the positive correlation

**Table 1** Predictive Values Involving Lipocalin 2 in Psoriasis

Subject	Population	Molecule Tested	Predictive Value	Ref.
Psoriasis patients	Psoriasis: n=37 Healthy control: n=17	Serum lipocalin 2	Higher serum lipocalin 2 levels indicate increased inflammation in the patients with psoriasis	[18]
Psoriasis patients	Psoriasis: n=37 Healthy control: n=15	Serum lipocalin 2	Lipocalin 2 conveys cardiovascular or metabolic risk in psoriatic patients	[56]
Psoriasis patients	Psoriasis: n=50 Healthy control: n=50	Serum lipocalin 2	Lipocalin 2 is correlated with baseline PASI and metabolic syndrome in psoriasis	[57]
Psoriasis patients	Psoriasis: n=30 Healthy control: n=30	Serum and tissular lipocalin 2	Tissue lipocalin 2 is more specific as a marker of psoriasis than serum lipocalin 2	[58]
Psoriasis and psoriatic arthritis patients	Psoriatic arthritis: n=50 Healthy control: n=36	Serum lipocalin 2	Lipocalin 2 can be used as positive markers in patients with psoriatic arthritis	[41]
Psoriasis and atopic dermatitis patients	Psoriasis: n=59 Healthy control: n=47	Serum lipocalin 2	Lipocalin 2 plasma concentration positively associated with itch intensity in psoriasis patients	[65]
Hidradenitis suppurativa (HS) and psoriasis patients	Psoriasis: n=11 HS: n=10 Healthy control: n=10	Serum lipocalin 2	Lower expression of lipocalin 2 accurately differentiate psoriasis from hidradenitis suppurativa	[73]

between them.<sup>58</sup> These arguments may indicate that tissue lipocalin 2 level is not related to the severity of the disease, but it may reflect a warning signal of excessive proliferation or metabolic disorders.

The therapeutic options for psoriasis consist of local therapy, systematic therapy, phototherapy, and biologic therapy. New treatment methods have been consistently explored and applied, with the aim of finding a final resolution for psoriasis, and they are shown in Table 2. Lipocalin 2 is a potential target for psoriasis treatment, and it mediates Tcf7l1 function. Thus, blocking lipocalin 2 can inhibit the Tcf7l1-lipocalin 2 pathway and subsequently terminate the proliferation of keratinocytes.<sup>34</sup> Moreover, the activation and infiltration of neutrophils also determine the progression of psoriasis. Because lipocalin 2 induces neutrophil chemotaxis and activation via the p38-MAPK and ERK-1/2 signaling pathways, inhibiting lipocalin 2 is also an effective method to modulate inflammation in psoriatic lesions.<sup>13</sup> For example, it was recognized that phototherapy with narrowband ultraviolet B (NBUVB) exerts its therapeutic function by decreasing the expression of lipocalin 2 in psoriatic lesions.<sup>24</sup> Recently, it was

**Table 2** Therapies Targeting Lipocalin 2 or Downstream Inflammatory Cytokines

Molecule or Treatment Tested	Route of Application	Subject	Therapeutic Effect	Ref.
Anti-lipocalin 2 mAb	Intraperitoneal injection	Imiquimod-induced mouse model	Alleviates skin lesions in psoriasis-like mice	[13]
Narrow-band ultraviolet B (NBUVB)	Direct exposure	Patients	Lower lipocalin 2 in lesion and PASI score after NBUVB treatment	[24]
DZ2002	Topical administration	Imiquimod-induced mouse model	Maintain epidermal keratinocyte differentiation and prevent dermal immune cell infiltration in psoriatic skin	[67]
miR-383	Cell transfection	HEK-293 T cells	Attenuate psoriasis-like symptoms, suppress inflammatory responses, cease keratinocyte proliferation, and promote apoptosis	[74]

found that methyl 4-(adenin-9-yl)-2-hydroxybutanoate (DZ2002) inhibits psoriatic inflammation by regulating the DNA methylation of the lipocalin 2 promoter, which further confirmed the therapeutic role of lipocalin 2 in psoriasis.<sup>67</sup> Moreover, it has been proved that neutralizing Tcf7l1 attenuates keratinocyte apoptosis and alleviates the effect of neutrophil aggregation and keratinocyte proliferation by decreasing lipocalin 2 and other downstream cytokines.<sup>34</sup> Hence, lipocalin 2 is a promising target for the treatment of psoriasis.

In biotherapy, mAbs such as anti-IL-17, IL-23, and TNF- $\alpha$  display high efficiency in psoriasis treatment.<sup>3</sup> Because there are several mAbs that distinctively inhibit different key cytokines, it is often unclear as to which one is the most optimal for treating a specific condition. The serum TNF- $\alpha$  level is positively associated with lipocalin 2, which suggests that patients with high serum lipocalin 2 levels are sensitive to anti-TNF- $\alpha$  mAb treatment.<sup>52</sup> Lipocalin 2 is also involved in the IL-23/IL-17 axis and plays an indispensable role.<sup>68</sup> Blocking IL-23 or IL-17 could also decrease the expression of lipocalin 2 and terminate its function in aggravating psoriatic diseases.

**Table 3** Features of Lipocalin 2 in Other Skin Diseases

Disease	Subjects	Molecule Tested	Effect of Lipocalin 2	Ref.
Skin squamous cell carcinomas (SCC)	Patients	Tissue lipocalin 2	High lipocalin-2 expression correlates with HPV positivity of cutaneous SCC	[75]
Skin squamous cell carcinoma	Xenograft mice model of SCC	Tissue lipocalin 2	High expression of lipocalin 2 drives tumor growth	[23]
Systemic sclerosis	Patients: n=50 Healthy control: n=19	Serum and tissue lipocalin 2	Serum lipocalin 2 levels positively correlated with skin score in patients with diffuse cutaneous SSC with disease duration of < 3 years	[76]
Skin wound	Mice wound models with diabetes	Skin lipocalin 2	Lipocalin 2 may facilitate macrophages polarization toward the M2 phenotype and improve impaired angiogenesis in diabetic wounds	[71]
Skin wound	Mice wound models with diabetes	Tissue and serum lipocalin 2	Lipocalin 2 is increased in wound and circulating neutrophils and may contribute to promote healing in diabetic wounds	[72]
Skin wound	Mice wound models	Tissue lipocalin 2	Lipocalin 2 promotes cell migration in vitro and wound healing in vivo	[21]
Severe acne	Acne subjects: n=15 Healthy control: n=15	Skin surface lipocalin 2	Activating lipocalin 2 in the skin may represent therapeutic alternatives to the use of isotretinoin in acne	[77]
Acne vulgaris	Patients: n=11 Healthy control: n=198	Tissue lipocalin 2	Stratum corneum lipocalin 2 may be useful as an objective biomarker of changes in acne vulgaris symptoms	[70]
Acne inversa	Patients: n=18 Healthy control: n=16	Serum and tissue lipocalin 2	Sera lipocalin 2 might be a biomarker for the inflammatory activity in acne inversa for it is positively correlated with Sartorius score and TNF- $\alpha$ blood levels	[52]
Hidradenitis suppurativa	Patients: n=29 Healthy control: n=9	Serum lipocalin 2	Lipocalin 2 level in serum can differentiate hidradenitis suppurativa subtypes	[78]

**Abbreviations:** IL, interleukin; IFN, interferon; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; MMP, matrix metalloproteinase; MCP, monocyte chemoattractant protein; IP, interferon-inducible protein; Tcf7l1, transcription factor 7-like 1; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase signaling pathways; DEFB, defensin beta; PsA, psoriatic arthritis; CXCL, chemokine (C-X-C motif) ligand; ERK, extracellular signal-regulated protein kinases; NBUVB, narrowband ultraviolet B; S100A7, S100 calcium binding protein A7; MMP, matrix metalloproteinase.



Beside psoriasis, lipocalin 2 is also a survival factor that decreases invasion and metastasis and promotes the oncogenesis process. Lipocalin 2 infiltrates into differentiated lesions and induces cell apoptosis by facilitating the lipocalin 2-mediated export of iron and reduction of ferritin.<sup>69</sup> In pityriasis rubra, lipocalin 2 is defined as a parakeratosis indicator that is absent in lichen planus, acute contact eczema, and basaloma.<sup>32</sup> It also has been considered as a biomarker to determine the inflammatory activity in acne vulgaris and acne inversa.<sup>52,70</sup> Furthermore, lipocalin 2 delivers its function in acne treatment with isotretinoin via facilitating the apoptosis of sebaceous gland cells.<sup>40</sup> Lipocalin 2 also highly expressed in wound and improve healing by promoting neutrophils migration and angiogenesis in wound lesion.<sup>21,71,72</sup> Obviously, lipocalin 2 participates in different skin diseases and exerts manifold functions, and they are shown in Table 3. Lipocalin 2 may become a promising treatment target of various skin diseases.

## Conclusions and Prospective Views

Lipocalin 2 is highly expressed in the skin lesions and blood of patients with psoriasis and is closely related to the severity of psoriasis. It not only stimulates various immune cells involved in the innate and adaptive immune responses to provoke inflammation via the IL-23/IL-27, p38-MAPK, and ERK-1/2 signaling pathways, but it also inhibits keratinocyte differentiation, thus leading to skin parakeratosis via the Tcf7l1-lipocalin 2 signaling axis. Moreover, lipocalin 2 could be a promising biomarker for predicting psoriasis severity and prognosis, and lipocalin 2 mAb could be an effect target for treating psoriasis. Blocking lipocalin 2 and its relevant signaling pathway may relieve the symptoms of psoriasis. Nevertheless, the pathogenesis of psoriasis is complicated, and inhibiting a single pathway is prone to fail, while extensively blocking several pathways may lead to an enormous cascade of side effects. Consequently, the functions of lipocalin 2 and the curative effects of anti-lipocalin 2 reagents require further investigation so that they can be developed into novel therapies for patients with psoriasis.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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