An update on the role of long non-coding RNAs in psoriasis

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Abstract

Increasing evidence suggests that long non-coding RNAs (lncRNAs) are of vital importance for various biological processes, and dysregulation of lncRNAs is frequently associated with various diseases such as psoriasis. LncRNAs modulate gene expression at the transcriptional, post-transcriptional, and translational levels; however, the specific regulatory mechanisms of lncRNAs in psoriasis remain largely unexplored. This review provides an overview of recent studies investigating mechanisms and functions of lncRNAs in psoriasis, especially focusing on the role of lncRNAs in keratinocytes, T cells, and dendritic cells.

Keywords: Long non-coding RNAs (LncRNAs); Psoriasis; Keratinocytes; T cells; Dendritic cells

Introduction

Psoriasis is a T cell-mediated chronic inflammatory skin disease characterized by epidermal hyperplasia, abnormal differentiation of keratinocytes (KCs), and excessive hyperplasia of blood vessels. The prevalence of psoriasis ranges from 0.09% to 11.43%, according to the 2016 report of the World Health Organization. In the United States, the annual economic burden of psoriasis is about $35.2 billion,[1] and comorbidities lead to higher medical costs.[2] A crucial causative factor in the onset of psoriasis is an imbalance in skin immune functions. The inflammatory process of psoriasis is primarily mediated by dendritic cells (DCs) and T cells, which interact with KCs and cause epidermal keratinization. The predominant pathological findings are incomplete keratinization, massive lymphocyte infiltration, and extensive skin angiogenesis at lesion sites. Local skin lesion inflammation during psoriasis is typically accompanied by a systemic inflammatory cascade, and comorbidities include disorders of the metabolic system, blood vessels, and the nervous system, as well as autoimmune disorders and systemic tumors. Moreover, psoriasis is frequently associated with adverse cardiovascular effects and hyperuricemia. Psoriasis and uricemia are ethnically specific, and the incidence of cardiovascular disease is 25% higher in psoriasis patients than in normal subjects.[3] In addition, the risk of chronic obstructive pulmonary disease in psoriasis patients increases with disease severity.[4] To date, the complex mechanisms underlying psoriasis have not been fully elucidated. Long non-coding RNA (lncRNA) is non-coding RNA longer than 200 nucleotides, which can participate in pre-transcriptional regulation such as histone modification and DNA methylation as well as transcriptional regulation regarding enhancer activities, transcriptional interference, regulatory transcription factors, variable splicing, competing endogenous RNA (ceRNA), other post-transcriptional regulation, and regulation of protein translation.[5] It has been shown that lncRNAs are frequently associated with tumor progression and cellular processes such as proliferation, apoptosis, and cell differentiation.[6,7] In psoriasis patients, research findings indicate that numerous differentially expressed lncRNAs (DE lncRNAs) play a crucial regulatory role at the gene level [Figure 1]. Psoriasis-associated dysregulated lncRNAs are listed in Table 1. This article reviews research on psoriasis-related lncRNAs.

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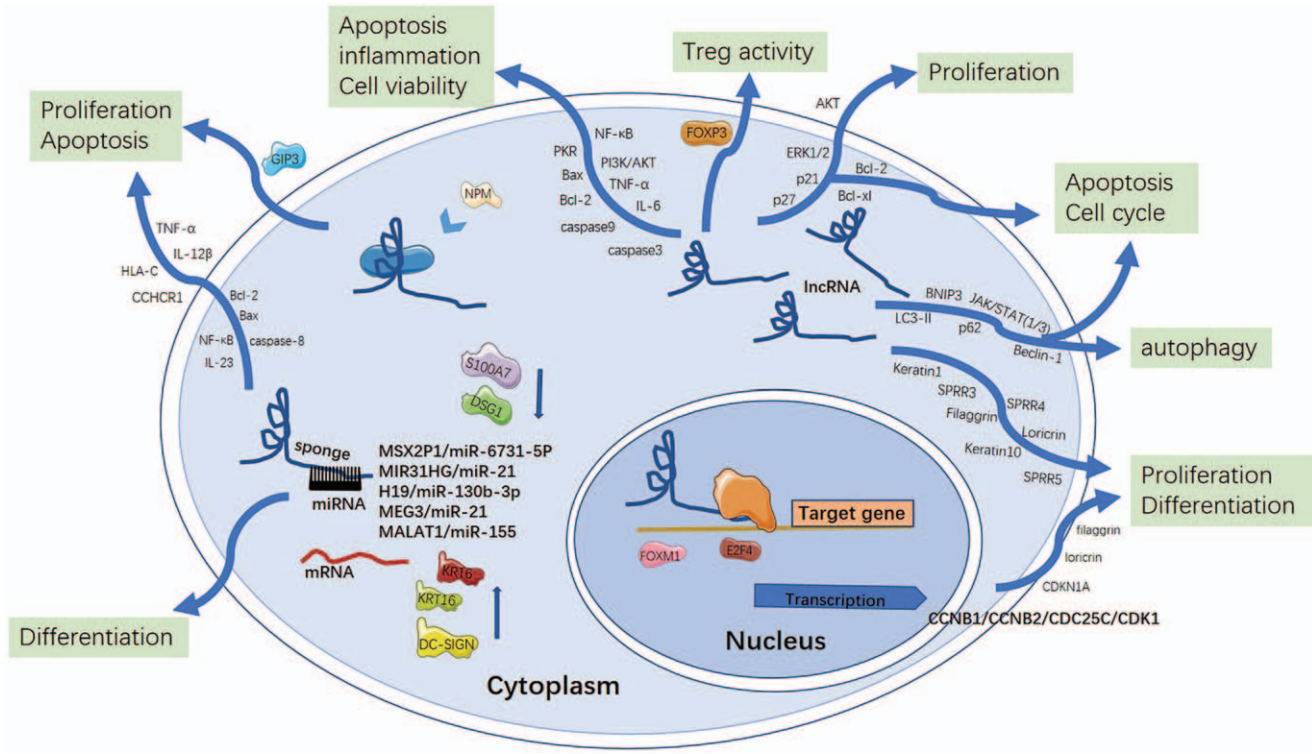

Figure 1: Roles of lncRNAs in the modulation of immunological mechanism of psoriasis. Navy blue lines are lncRNAs; irregular circles represent target proteins; the light green rectangle means that the biological process. AKT: Protein kinase B; CCHCR1: Coiled-coil alpha-helical rod protein 1; ERK: Extracellular signal-regulated kinase; HLA: Human leukocyte antigen; IL: Interleukin; lncRNAs: Long non-coding RNA; JAK: Janus kinase; NF: Nuclear factor; NPM: Nucleophosmin; PKR: Protein kinase R; STAT: Signal transducer and activator of transcription; TNF: Tumor necrosis factor.

Table 1: Characteristics of lncRNAs in psoriasis.

LncRNAs	Tissue/cell	Expression	Regulating mechanisms	References
lncRNA-MSX2P1	Skin/HaCaT	Up-regulated	Promote proliferation and suppress apoptosis	Qiao *et al* Exp Cell Res 2018[11]
MIR31HG	Skin/HaCaT	Up-regulated	Promote proliferation	Gao *et al* Biol Res 2018[15]
lncRNA-H19	Keratinocyte	Up-regulated	Promote differentiation	Li *et al* Cell Death Dis 2017[16]
lncRNA-RP6-65G23.1	HaCaT	Up-regulated	Promote proliferation and suppress apoptosis	Duan *et al* J Cell Biochem 2020[17]
MEG3	Skin/HaCaT	Down-regulated	Suppress proliferation and promote apoptosis	Jia *et al* BMC Mol Cell Biol 2019[14]
PRINS	Skin/keratinocyte/ HaCaT	Up-regulated	Promote proliferation and suppress apoptosis	Szegedi *et al* Exp Dermatol 2010[13]; Bari *et al* Arch Dermatol Res 2011[18]; Szegedi *et al* Int J Mol Sci 2012[21]
HOTAIR	HaCaT	Up-regulated	Promote apoptosis and inflammation	Liu *et al* Braz J Med Biol Res 2018[22]
lncRNA HULC	HaCaT	Up-regulated	Promote apoptosis and autophagy	Zhao *et al* Biomed Pharmacother 2018[24]
PRANCR	Keratinocytes	Up-regulated	Promote proliferation and differentiation	Cai *et al* Genome Res 2020[26]
LINC00941	Keratinocytes	Down-regulated	Suppress proliferation and differentiation	Ziegler *et al* EMBO Rep 2019[27]
AF005081,UC003af, BC020554	Keratinocytes	Up-regulated	–	Mazar *et al* Mol Genet Genomics 2010[28]
lncRNA FLICR	T cell	–	Suppress Treg activity	Zemmour *et al* Proc Natl Acad Sci U S A 2017[38]
LncRNA MALAT1	DC	–	Promote the expression of DC-SIGN	Wu *et al* Front Immunol 2018[45]
PSORS1C3	Skin	Up-regulated	–	Holm *et al* Acta Derm Venereol 2005[46]
ANRIL	Skin	–	–	Rakhshan *et al* Int Immunopharmacol 2020[54]
CARD14	Skin	Up-regulated	–	Gupta *et al* J Invest Dermatol 2016[58]
LNC-AP000769.1-1: 2, ENST00000557691 and LNC-HSFY2-10: 1	Skin	Up-regulated	–	Yan *et al* Mol Med Rep 2019[59]
LNC-MGMT-2:1, LNC-POLR3E-3:3, LNC-THRSP-6: 1 and LNC-PERP-2: 7	Skin	Down-regulated	–	Yan *et al* Mol Med Rep 2019[59]
AL035425.3 and PWAR6	Skin	Down-regulated	–	Zhou *et al* Exp Ther Med 2019[60]

LncRNAs: Long non-coding RNAs; DC: dendritic cells.

LncRNAs and Psoriasis

LncRNAs and KCs

KCs are a primary type of epidermis cells and have strong proliferation and differentiation capabilities, which is crucial for skin renewal, barrier, and immune functions. During psoriasis, hyperplasia leads to hypertrophy and keratinization, which is associated with abnormal KC proliferation and apoptosis. The characteristic signs of KC hyperproliferation and abnormal differentiation during psoriasis are as follows: changes in expression of core proteases and genes in the epidermal differentiation complex; significant down-regulation of the late KC differentiation markers such as cysteine-containing aspartate proteolytic enzyme-14; up-regulation of the early KC differentiation marker coat protein; reduction in K1 and K10 expression; and abnormally high expression of K6, K16, and K17 in psoriatic lesions.[8] Psoriasis-specific differentially expressed genes (DEGs) occur in KCs and are induced by interleukin (IL)-17A.[9] Excessive polyamine production in psoriatic KCs was found to facilitate endocytosis of RNA by myeloid DCs and thereby promote TLR7-dependent RNA induction and IL-6 production.[10]

Expression of lncRNAs in clinical psoriatic lesions

Expression levels of LncRNA-MSX2P1 were found to be higher in psoriatic skin lesions than in normal skin tissue.[11] Using RNA sequencing, MIR31HG and lncRNA-RP6-65G23.1 were reported to be up-regulated in the epidermis of psoriasis patients.[12] Psoriasis Susceptibility-Related RNA Gene Induced by Stress (PRINS) is a non-coding RNA which is overexpressed in psoriatic and non-lesioned epidermis, and its expression is induced by stress, suggesting that overexpression of PRINS in non-lesioned psoriatic epidermis may play a role in psoriasis susceptibility rather than in the formation of psoriatic lesions.[13] In contrast, compared with normal skin tissue, expression of materally expressed gene 3 (MEG3) was significantly down-regulated in skin tissue of psoriasis patients.[14]

LncRNAs regulate KC proliferation, apoptosis, and inflammation during psoriasis

mRNA levels of MSX2P1 were found to increase significantly after treatment with IL-22 in HaCaT and HNEK cells. The authors selected a "MSX2P1-miR-6731-5p-S100A7" ceRNA network for further research and observed a positive correlation between MSX2P1 expression and S100A7 expression. A luciferase reporter assay confirmed that MSX2P1 directly targeted miR-6731-5p and down-regulated expression of miR-6731-5p, which promotes proliferation, suppresses apoptosis in IL-22-stimulated KCs and increases expression of S100A7, IL-12β, IL-23, human leukocyte antigen (HLA)-C, coiled-coil alpha-helical rod protein 1, tumor necrosis factor (TNF)-α, and nuclear factor (NF)-κB proteins. Taken together, lncRNA-MSX2P1 can function as an endogenous sponge RNA by directly binding miR-6731-5p; this leads to an increase in S100A7 and other pro-inflammatory cytokines by inhibiting expression of miR-6731-5p and activating S100A7 in KCs stimulated by IL-22, which facilitates the manifestation of psoriasis.[11]

Knockdown of MIR31HG was observed to inhibit HaCaT KC proliferation, which may be due to the induction of a G2/M phase arrest. After stimulating KCs with IL-17A, IL-22, TNF-α, and IL-1α, which activated nuclear factor-kappa B (NF-κB) signaling, MIR31HG expression increased. Low expression of p65 siRNA, which is a subtype of NF-κB, led to a significant decrease in MIR31HG expression induced by cytokines (IL-17A, IL-22, TNF-α, or IL-1α). Similarly, decreased expression of MIR31HG was observed in HaCaT KCs treated with an NF-κB inhibitor. These findings suggest that MIR31HG knockdown inhibits proliferation of HaCaT KCs, whereas expression of MIR31HG depends on activation of NF-κB. MIR31HG thus plays a decisive role in the regulation of excessive proliferation of psoriatic KCs and may be a potential therapeutic target.[15]

LncRNA H19 contained two miRNA-130b-3p binding sites. While miRNA-130b-3p substantially reduced luciferase activity of H19-containing wild type (WT), it attenuated luciferase activity of the H19 mutant form. Overexpression of miRNA-130b-3p in KCs led to down-regulation of H19 expression. During KC differentiation, expression of H19 increased, while expression of miR-130b-3p was down-regulated. H19 knockdown, which reduces expression of DSG1, was found to reduce the levels of KCs upon calcium stimulation. H19 attenuated inhibitory effects of miR-130b-3p on DSG1 expression. In the presence of DSG1 targeted protector, the inhibitory effect of H19 knockdown on KC differentiation was alleviated. Taken together, lncRNA-H19 may act as an endogenous sponge by directly binding miR-130b-3p and thereby inhibiting its activity against DSG1 and promoting KC differentiation, thus it may constitute a new target for the treatment of psoriasis.[16]

In KCs stimulated with a cytokine M5 mix (including IL-17A, oncostatin-M, TNF-α, IL-22, and IL-1α), expression of RP6-65G23.1 increased more than five-fold, compared to the control. Knockdown of RP6-65G23.1 significantly inhibited cell proliferation, promoted apoptosis, and induced G1/S phase growth arrest, while overexpression of RP6-65G23.1 showed the opposite effects. Protein kinase B (AKT) and extracellular signal-regulated kinase (ERK)1/2 are essential regulators of cell proliferation and survival. In HaCaT cells, down-regulation of RP6-65G23.1 expression inhibited activity of AKT and ERK1/2 signaling pathways. Expression of anti-apoptotic Bcl-2 and Bcl-xL proteins was down-regulated in RP6-65G23.1-depleted HaCaT cells and was up-regulated in RP6-65G23.1-overexpressing cells.

In summary, lncRNA-RP6-65G23.1 facilitates KC proliferation by activating the AKT and ERK1/2 pathways, which affects the G1/S process. In addition, it may regulate KC apoptosis by up-regulating the expression of Bcl-2 and Bcl-xl proteins, thereby increasing the probability of developing psoriasis.[17]

MEG3 was found to be significantly down-regulated in human immortalized keratinocytes (HaCaT) and normal human epidermal keratinocytes (NHEKs) cells. Low expression of MEG3, which promotes proliferation of

Act-HaCaT and Act-NHEKs, decreased expression of caspase-8 and Bax and increased expression of Bcl-2 protein which inhibits apoptosis. A dual luciferase reporter assay demonstrated direct binding of miR-21 by MEG3. Overexpression of MEG3 significantly reduced expression levels of miR-21. Therefore, lncRNA MEG3 may be a competitive endogenous substance of miR-21 during psoriasis. In Act-HaCaT and Act-NKEK, overexpression of miR-21 reverses the decrease in cell proliferation rates, increases apoptosis rates, increases caspase-8 and Bax expression, and decreases Bcl-2 expression caused by overexpression of MEG3. A dual luciferase reporter assay revealed the binding site of caspase-8 and miR-21. Several downstream proteins of caspase-8, cleaved caspase-8, cytc, and apaf-1 are regulated by miR-21 and MEG3. In summary, MEG3 may alleviate excessive proliferation and insufficient apoptosis of psoriatic KCs by regulating miR-21 and caspase-8 expression.[14]

One of the genes regulated by PRINS ncRNA, G1P3, is an interferon-induced gene with anti-apoptotic effects in cancer cells. *In vitro*, G1P3 protein levels are the highest in proliferative KCs, and down-regulation of G1P3 leads to increased apoptosis rates. Loss of control of PRINS ncRNA may be associated with the pathogenesis of psoriasis and may reduce the sensitivity to spontaneous KC apoptosis by regulating G1P3.[13] Silencing PRINS exerted no effect on NF-κB activity of lipopolysaccharides (LPS)-induced HaCaT cells and NHKs, indicating that PRINS may affect the function of KCs independently of NF-κB signaling.[18] Studies have shown that in UVB-treated fibroblasts and cancer cells, nucleophosmin (NPM) is transported into the nucleus. Similar translocation of NPM in KCs cultured under UVB radiation was detected.[19,20] Knockout of the *PRINS* gene causes NPM to remain in the nucleoli of KCs irradiated with UV-B, indicating that PRINS may differentially affect regulation of proliferation and differentiation of cells as well as stress responses.[21]

HOX antisense intergenic RNA (HOTAIR), a recently discovered lncRNA that plays a critical role in gene regulation and chromatin dynamics, was highly expressed in HaCaT cells after 16 h of UVB irradiation. In UVB-treated HaCaT cells, overexpression of HOTAIR significantly reduced survival rates of cells, increased apoptosis, inhibited expression of Bcl-2 protein, and promoted the production of apoptosis-related factors (Bax, caspase3, and 9), TNF-α, and IL-6 protein expression. Overexpression of HOTAIR inhibited cell viability, improved apoptosis, and increased protein expression of TNF-α and IL-6. Moreover, HOTAIR also increases expression of RNA-dependent protein kinase R (PKR) mRNA. HOTAIR overexpression reduced cell viability after UVB treatment by increasing PKR and increased apoptosis rates and protein expression of the inflammatory factors TNF-α and IL-6. PKR overexpression activated the PI3K/AKT and NF-kB pathways. Therefore, HOTAIR plays an essential role in promoting UVB-induced apoptosis and inflammatory damage by up-regulating KC PKR.[22]

In a previous study, highly up-regulated in liver cancer (HULC) was the first lncRNA which was found to be highly expressed in hepatocarcinoma cells.[23] In UVB-treated HaCaT cells, HULC expression levels were significantly higher than those in the control group. HULC knockdown increased cell viability and decreased apoptosis rates; however, expression of LC3-II and Beclin-1 was markedly down-regulated, and expression of p62 protein was significantly up-regulated. HULC overexpression suggested the opposite effect. mRNA and protein levels of Bcl-2 interacting protein 3 (BNIP3) decreased when HULC was knocked down in UVB-treated HaCaT cells. JAK/STAT (1/3) inhibitor (ZM 39923) markedly inhibited up-regulation of p-JAK-1, p-STAT-1, p-STAT-3, and BNIP3 protein caused by overexpression of HULC. In UVB-stimulated HaCaT cells, HULC overexpression resulted in decreased apoptosis rates after treatment with the autophagy inhibitor 3-MA. In UV-stimulated HaCaT cells treated with JAK/STAT (1/3) inhibitor (ZM 39923), HULC overexpression and low BNIP3 expression led to reduced apoptosis rates. UVB treatment reduced HaCaT cell viability, increased apoptosis and autophagy, and up-regulated expression of HULC. HULC overexpression reduced activity of the JAK/STAT (1/3) signaling pathway, reduced cell viability, promoted apoptosis and autophagy, and up-regulated BNIP3 mRNA and protein levels. In conclusion, lncRNA HULC up-regulated BNIP3, activated the JAK/STAT (1/3) signaling pathway, and accelerated UVB-induced HaCaT cell damage. This study provides a feasible target for the clinical treatment of UVB-induced KC injury.[24]

Knockdown of the *PRANCR* gene was found to inhibit KC proliferation and reduce cloning ability; however, it had no effect on KC apoptosis. In primary KCs lacking PRANCR, 1136 DEGs were identified, and expression of 927 genes was reduced. A total of 209 up-regulated genes were enriched in several pathways, most notably genes related to mitogen-activated protein kinase (MAPK) pathway signaling. The analysis tool Enrichr was used to determine that E2F4 and FOXM1 were transcription factors of PRANCR. *PRANCR* gene knockout in primary KCs elicited significant down-regulation of the target gene of transcription factor E2F4. Moreover, expression of cell cycle genes with CHR sites was indirectly inhibited by TP53 through CDKN1A and E2F4 which are collectively known as the TP53-CDKN1A-DREAM-CHR pathway.[25] In PRANCR-deficient primary KCs, expression of 210 genes in the P53-CDKN1A-DREAM-CHR pathway was strongly suppressed. Furthermore, the *TP53-DREAM* genes involved in the G2/M checkpoint control, that is, CHEK2, CDK1, CCNB1, CCNB2, and CDC25C were also down-regulated by PRANCR knockdown. In primary human fibroblasts, PRANCR knockdown resulted in impaired proliferation and reduced expression of the G2/M checkpoint control genes CCNB1, CCNB2, CDC25C, and CDK1. In primary KCs which expressed PRANCR at low levels, TP53 and E2F4 protein expression was relatively unchanged, CDKN1A protein expression increased, and expression in the nucleus was also higher. In summary, PRANCR regulates KC proliferation and cell cycle progression. Transcriptome analyses showed that PRANCR controlled expression of 1136 genes and strongly enriched expression of late cell cycle genes containing CHR promoter elements. In addition,

PRANCR deletion can lead to increased total CDKN1A and nuclear CDKN1A (p21) levels, and these factors control KC proliferation and differentiation. These observations suggest that PRANCR is an lncRNA which regulates epidermal homeostasis; moreover, also other candidate lncRNAs which may play a role in this process were identified.[26]

Transcriptome sequencing analyses revealed that expression of LINC00941 which is encoded on chromosome 12 was highest in undifferentiated precursor KCs and was significantly reduced at the beginning of terminal differentiation. In KCs, LINC00941 knockdown resulted in increased mRNA levels of the early differentiation gene *KRT1* and of the late differentiation gene *SPRR3* and of filaggrin. In LINC00941-deficient human epidermal tissue, mRNA and protein abundance of the early differentiation gene *KRT10*, of late differentiation gene *SPRR4*, and of loricrin were increased. In undifferentiated primary human KCs, 28 well-characterized genes critical to epidermal differentiation and located in the epidermal differentiation complex were prematurely expressed in LINC00941-knockout epidermis, including 16 of 18 *LCE* genes, the loricrin gene, and *SPRR4*. SPRR5 was almost not detected. However, SPRR5 expression levels increased significantly after the onset of epidermal differentiation and reached the highest levels at late differentiation stages. In KCs and human organoid epidermis, SPRR5 knockdown resulted in a decrease in mRNA and protein abundance of early and late differentiation genes (*SPRR3*, *KRT1*, *FLG*, and *LOR*). In total, expression of 54.8% of 126 genes that were suppressed in SPRR5-deficient epidermal tissues was induced in LINC00941-deficient organ-type epidermis. In human KCs, double-deletion of LINC00941 and SPRR5 resulted in decreased levels of keratin 1 and filaggrin. SPRR5 considerably differs from other members of the human SPRR family regarding phylogeny and its function as an indispensable regulator of human epidermal differentiation. RNA sequencing revealed the importance of LINC00941 and SPRR5 for maintaining appropriate epidermal homeostasis. Compared with mRNA, the nuclear concentration of LINC00941 was increased, and its role in inhibiting premature activation of *LCE* and *SPRR* gene clusters was identified.

In summary, lncRNA LINC00941 is an important regulator of human epidermal homeostasis. It is enriched in precursor KCs and inhibits KC differentiation. LINC00941 can inhibit expression of SPRR5, a positive regulator of KC differentiation. In LINC00941-deficient organic epidermis, expression of 54.8% of the genes suppressed in SPRR5-deficient epidermal tissues was induced, suggesting that LINC00941 and SPRR5 share a common mode of action. These observations provide insights into to the highly complex regulatory network of epidermal homeostasis, which is crucial for understanding the molecular basis of epidermal development and skin diseases.[27]

A novel ncRNA array platform was developed using Invitrogen/Life Technologies Corporation to identify lncRNAs in KCs, and AF005081 and UC003af were found to be up-regulated only at 120 h, while BC020554 was only up-regulated in submerged epidermal equivalents and was down-regulated upon differentiation. A third expression change pattern was observed in lncRNA AK022798, and expression was lower during the submerged phase but was up-regulated during early differentiation and then gradually decreased during the transformation process; however, further experiments are needed to identify the functions of these lncRNAs.[28]

LncRNAs and T cells

One of the pathological characteristics of psoriasis is the activation of the Th1/Th2 axis and abnormal balance of Th17 and regulatory T (Treg) cells.[29] Th1 and Th2 are the first discovered $CD4^+$ T cell subsets which are characterized by secretion of interferon (IFN)-γ and IL-4, respectively.

Without affecting the activity of IFN-γ, the use of anti-IL-23 p19 Guselkumab at the highest dose resulted in a psoriatic area and severity index reduction rate of more than 75% in all patients,[30,31] suggesting that Th1 cell-related IFN-γ plays a major role in the initiation and pathogenesis of psoriasis; however, it is not a core factor during chronic inflammation. Th2 cell-specific cytokine IL-4 can completely block the function of IL-23, which can lead to Th17 cell activation and differentiation. Therefore, IL-4 can inhibit the inflammatory response mediated by Th17 cells, which improves skin lesions in psoriatic patients.[32]

During psoriasis, Th17 cells exert their effects by secreting IL-17A, IL-17F, IL-26, and TNF, forming a feedforward inflammation network with KCs, activating STAT-1 and NF-κB signaling pathways, and inducing secretion of proinflammatory factors from KCs. At present, most studies are focused on the role of IL-17A in psoriasis. IL-17A can inhibit KC differentiation and promote KC proliferation by down-regulating the regenerating islet-derived protein 3 alpha, and it stimulates KCs to produce antimicrobial peptides, which causes more inflammatory cells to infiltrate.[33] Currently, it remains controversial whether the number of Treg cells changes during psoriasis. Studies have revealed that the number of Treg cells in peripheral blood and tissues of psoriasis patients is significantly increased and is positively correlated with the severity of the disease.[34] However, the number of Treg cells in peripheral blood of psoriasis patients decreased, which can be counteracted by anti-TNF-α treatments.[35] Chen *et al*[36] found that expression levels of IL-21 in CD4 + T cells derived from patients were higher *in vitro*, which can promote differentiation and proliferation of Th17 cells and inhibit differentiation of Tregs, causing an imbalance of Th17/Treg cells.

Expression of lncRNAs in clinical psoriatic lesions

PRINS was found to be highly expressed in non-lesioned psoriatic epidermis (24-fold higher than in normal epidermis). The abundance of PRINS transcripts in psoriatic plaques did not reach the levels observed in non-lesioned psoriatic epidermis; however, it was significantly higher than that in healthy epidermis (12-fold). Epidermal specimens from healthy patients and psoriasis patients were treated with a mixture of T cell lymphokines, IFN-γ, and IFN-γ + IL-3 + granulocyte-macrophage colony-stimulating factor. T cell lymphokine therapy

exerted no substantial effect on PRINS expression in healthy epidermis, whereas in untreated psoriatic epidermis, PRINS expression was five-fold reduced after treatment with a T-lymphokine mixture. The level of PRINS in non-skin lesions of psoriasis was reduced, but it was not expressed in normal epidermis due to the effects of T lymphokines, suggesting that PRINS overexpression plays a role in susceptibility to psoriasis rather than merely in psoriasis symptoms.[37]

Regulation of lncRNA expression in FLICR knockout mice

In the ImmGen compendium of immunocyte gene expression, only lncRNA foxp3 long intergenic noncoding RNA (FLICR) was detected in Treg cells. FLICR and Foxp3 occurred in combination, but only during the final stage of CD25hi in the process of Treg differentiation. Ppp1r3f and Foxp3 transcripts increased slightly in FLICR-deficient mice. Treg cell differentiation and homeostasis did not seem to change, with normal proportions of Treg in the thymus, spleen, and lymph nodes. Compared with wild-type mice, FLICR knockout mice showed tighter Treg distribution. Down-regulation of FoxP3 (FoxP3^{lo}) in CD4$^+$ T cells significantly decreased Treg cells.[38]

LncRNAs modulate T cell-mediated immune dysfunctions

FLICR, which was present in Treg cells in all peripheral lymphoid organs, was found at lower levels in specific Treg cell populations occurring in several non-lymphoid tissues. A decrease in FoxP3^{lo} cells was observed in Treg cells transfected with locked nucleic acids, confirming a direct effect of FLICR RNA on FoxP3 expression. Higher FLICR levels were observed in cells with lower FoxP3 levels. FoxP3^{lo} cells that usually appeared in low IL-2 cultures were essentially absent in Treg cell cultures of FLICR knockout mice. IL-2 reduced the expression of FLICR in cell cultures. A ChIP sequencing analysis of human Treg cells[39] showed slight STAT5b accumulation in the FLICR promoter region, indicating that IL-2 may directly inhibit the FLICR pathway. Characteristic genes that were overexpressed in Treg cells tended to be underexpressed in wild-type cells, and the transcripts most affected by FLICR deletion were Treg cell-characteristic genes. Similarly, expression of FoxP3 binding genomic targets in wild-type Treg cells was mostly lower than that in KO Treg cells. Compared with wild-type FLICR mice, transgenic FLICR cannot restore FoxP3^{lo} Treg cells *in vivo*, nor can it restore sensitivity to low IL-2 supply *in vitro*. FLICR lncRNA, which acted as a negative regulator, regulated Foxp3 expression, resulting in decreased FoxP3 protein levels in the Treg cell subpopulation. In absence of IL-2, the effect of FLICR was particularly conspicuous. By contrast, IL-2 inhibits FLICR expression.

In the mouse and human genomes, FLICR is adjacent to Foxp3 and is expressed particularly in mature Treg cells, however, it only plays a role in the cis gene. FLICR changes the chromatin accessibility of the conserved non-coding sequence 3/accessible region 5 region of Foxp3. Stability of Foxp3 is essential for maintaining the dynamic balance of Treg cells and preventing autoimmunity. FLICR lncRNA down-regulates Foxp3 expression and inhibits Treg activity, which indirectly exacerbates psoriasis.[38]

LncRNAs and DCs

DCs, as antigen-presenting cells, act as a bridge connecting innate and adaptive immune responses. DCs not only stimulate activated effector T cells and memory T cells, but also induce activation and proliferation of T cells. A large number of plasmacytoid dendritic cells (pDCs), mature and immature DCs, and inflammatory dendritic epithelial cells, among others, occur in psoriatic lesions.[40] Furthermore, interactions between DCs and CD4$^+$ and CD8$^+$ T cells in psoriatic epithelial tissue may stimulate activation of the latter and produce proinflammatory mediators leading to the onset of psoriasis.[41]

LncRNAs regulating immune tolerance in DCs

MALAT1 lncRNA, originally discovered in tumors, was recently reported to be associated with innate immune responses.[42,43] In DCs, MALAT1 expression peaked 12 h after LPS stimulation. ChIPBase (http://rna.sysu.edu.cn/chipbase/) was used to predict the two potential binding sites of NF-κB p65, which is a key mediator and transcription factor involved in stimulation of MALAT1 promoter points -1537 and -1037. In LPS-stimulated DCs, PDTC, which is an inhibitor of NF-κB, can significantly reduce MALAT1 expression. Similarly, SC-514, which is an IKK2 inhibitor, can inhibit p65-related transcriptional activation of the NF-κB pathway.

In LPS-stimulated MALAT1-suppressed DCs, the protein levels of CD80, CD86, and MHCII increased, and overexpression of MALAT1 produced the opposite result.

After inducing MALAT1 expression in LPS-stimulated DCs, protein levels of the proinflammatory cytokines IL-6, IL-12, and IFN-γ decreased, and mRNA levels of anti-inflammatory cytokine IL-10 increased significantly.

Compared with LPS-DC co-cultures, the proliferation ability of T cells co-cultured with DCs expressing high levels of MALAT1 was reduced. When MALAT1-overexpressing DCs were co-cultured with T cells, the number of Treg cells was significantly higher than that of LPS-DCs. Remarkably, Treg cells of MALAT1-overexpressing DCs (from BALB/c mice) exhibited suppression of T cell proliferation in presence of DCs as stimulators, but not in presence of DCs from normal mice, whereas no marked difference in T cell proliferation occurred between DCs induced by various types of LPS. These findings confirmed that MALAT1-overexpressing DCs were tolerant, which impaired activation of effector T cell responses and induced formation of Treg cells with antigen-specific inhibition.

DC-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN), an immunomodulatory receptor, plays a paramount role in DC immune responses and T cell activation by selectively up-regulating IL-10. In DCs, overexpression of MALAT1 resulted in a significant

increase in DC-SIGN mRNA levels; however, the opposite effect was observed after MALAT1 knockdown. The combination of MALAT1 overexpression and DC-SIGN knockdown led to a significant increase in the number of costimulatory molecules, compared with only MALAT1-overexpressing DCs; however, no significant difference compared to control DCs was observed.

Suppression of the initiated T cell response was markedly stronger in DC-SIGN$^+$ DCs than in LPS-stimulated DCs and DC-SIGN$^-$ DCs. DC-SIGN $^+$ DCs induced generation of Treg cells, in contrast to LPS-DCs and DC-SIGN$^-$ DCs. In addition, IL-10 mRNA levels in Treg cells induced by DC-SIGN$^+$ were significantly higher than those in Tregs cells induced by LPS-DCs or DC-SIGN$^-$.

MALAT1 was significantly enriched in Ago2 immunoprecipitate, compared with IgG control immunoprecipitate, indicating that MALAT1 may be regulated by ceRNA. Starbase screening revealed that the MALAT1 sequence contained three possible binding sites to bind miR-155, that is, WT1 (4467-91), WT2 (5031-51), and WT3 (5375-98), and miR-155 was also observed in Ago2 immunoprecipitate. After MALAT1 knockout, miR-155 expression in DCs is up-regulated. It was reported that DC-SIGN was indirectly targeted by miR-155 by directly inhibiting PU1.[44] MALAT1 knockout significantly reduced the levels of PU.1 and DC-SIGN proteins in DCs, and miR-155 mimics partially undid the effects of MALAT1 on PU.1 and DC-SIGN protein levels.

DCs, which are parts of dermal microvascular units, are derived from bone marrow hematopoietic stem cells. As the predominant antigen-presenting cells of the human immune system, DCs can affect activation of T cells and the development of chronic inflammation, and MALAT1 expression was up-regulated in DCs. MALAT1 plays a regulatory role in promoting DC tolerance and in inducing immune tolerance *in vivo* and *in vitro*. MALAT1 promoted DC-SIGN expression by acting as an miR-155 sponge, which is essential for the maintenance of DC tolerance and for increased tolerance of the DC-SIGN $^+$ subgroup.[45]

LncRNAs as potential biomarkers of psoriasis

The psoriasis susceptibility 1 candidate 3 gene (*PSORS1C3*) was recently identified using Basic Local Alignment Search Tools, express sequence tag, and 5′ and 3′ rapid-amplification of cDNA end. PSORS1C3 RNA transcripts of the expected size were part of the total RNA of normal skin, tonsils, psoriatic skin lesions, and non-cutaneous skin lesions. Pyrosequencing revealed a total of 11 single nucleotide polymorphisms (SNPs) in PSORS1C3, of which SNP 15721489 was most strongly correlated with psoriasis. When stratifying all SNPs, HLA-Cw*0602 produced a strong correlation with psoriasis; however, when stratifying HLA-Cw*0602 only, none of the PSORS1C3 SNPs were correlated with psoriasis. The correlation of psoriasis and various SNPs was suggested to be due to a linkage imbalance with HLA-Cw*0602. Taken together, PSORS1C3 was detected in normal and psoriatic skin, and a total of 11 SNPs were discovered using coding region sequencing. Three SNPs were found to be significantly correlated with psoriasis. Due to a linkage disequilibrium, this association seemed to depend on HLA-Cw*0602.[46] Further research is required to confirm potential regulatory effects of PSORS1C3 during psoriasis.

Antisense non-coding RNA in the INK4 locus (ANRIL) is linked to the risk of immune-related diseases and coronary artery disease.[47,48] *CASP14* is one of the genes regulated by ANRIL, and it is involved in inflammatory and apoptosis processes and in the pathogenesis of psoriasis.[49] Four ANRIL SNPs (rs1333045, rs1333048, rs4977574, and rs10757278) were selected, which have been shown to play a role in immune-related diseases and appeared to be related to cancer risk,[50-53] for genotype analyses in patients with psoriasis and in healthy controls. In all inheritance models, rs1333048, rs4977574, and rs10757278 were associated with psoriasis risk, and rs1333045 was not associated with psoriasis. Compared with the control group, the C allele of SNP rs1333048 was more prevalent in psoriasis patients. Moreover, the A allele of rs4977574 exerted protective anti-psoriatic effects, and the G allele of rs10757278 may be associated with a higher risk of psoriasis. C-A-G-A haplotypes (rs1333045, rs1333048, rs4977574, and rs10757278, respectively) were psoriasis-protective haplotypes, and C-A-G-G and T-C-G-G haplotypes were psoriasis risk factors.

Genotyping of four SNPs (rs1333045, rs1333048, rs4977574, and rs10757278) was performed in 286 psoriasis patients and 300 age/sex-matched controls to determine the role of ANRIL as a risk factor for psoriasis; however, further studies are required to verify whether this is associated with immune responses.[54]

A total of 263 DE lncRNAs were identified using 18 psoriasis lesion samples and 16 healthy control samples in the RefSeq database. Of these, 109 were highly expressed and 154 were expressed at low levels. The RefSeq database, the GENCODE lncRNA set, and the data of Hangauer *et al*[55] were used to compile a reference database consisting of 67,157 lncRNAs. Using this database, 62,826 expressed lncRNAs were observed. Compared with the control group, 971 lncRNAs were DEGs during psoriasis, 572 of which were overexpressed. qPCR revealed that the three lncRNAs TRHDEAS1, CYP4Z2P, and HINT1 were differentially expressed in psoriatic skin lesions, which was in line with RNA sequencing results. Twenty-eight of the top-30 overexpressed lncRNAs in the combined database were also observed by Li *et al*,[56] as were 27 of the top-30 lncRNAs expressed at low levels. In total, 157 DE lncRNAs were identified in the skin of psoriasis patients before and after anti-TNF-α monoclonal antibody adalimumab treatment. A total of 377 DE lncRNAs occurred in the skin of healthy subjects after treatment with adalimumab. Comparison of the expression of GENCODE lncRNAs and RefSeq mRNA transcripts revealed that 933 lncRNAs were highly correlated with 1143 protein-coding genes.

CARD14 lncRNA was observed to be overexpressed in psoriatic lesions overlapping with *CARD14*, a gene involved in NF-κB activation, by examining 36 known and newly discovered psoriasis gene loci reported by Tsoi

et al.[57] The authors used the web-based RNAsnp tool to predict that CARD14 SNP rs9902358 can cause significant changes in the secondary structure of CARD14 lncRNA. The other two DE lncRNAs associated with psoriasis are LINC00302 and IL12RB2 with the SNPs rs6677595 and rs9988642, respectively. However, the functions of the three above-mentioned lncRNAs during psoriasis require further research.[58]

LncRNA microarray results showed that 2194 lncRNAs were dysregulated in psoriatic lesions and in normal tissues, 1123 of which were up-regulated and 1071 were down-regulated. Using hierarchical cluster analysis to rank the samples according to expression levels, LNC-SLC6A14-1:1 was found to occur at the highest expression levels, and NONHSAT044111 was the least-expressed lncRNA. Based on the results of a microarray, a total of 1725 mRNAs with abnormal expression were identified, 1157 of which were overexpressed, and 568 were down-regulated. The lncRNA DEFB4A occurred at the highest expression levels and WIF1 at the lowest levels. Target genes of 1549 dysregulated lncRNAs were predicted using a target prediction software. Among them, 1447 dysregulated lncRNAs had cis-regulated target genes, 397 dysregulated lncRNAs had trans-regulated target genes, and 295 dysregulated lncRNAs had trans- and cis-regulated target genes. It is worth noting that 3740 mRNAs are regulated by dysregulated lncRNAs. Among them, 1460 mRNAs may be regulated in cis, 2588 mRNAs in trans, and 308 mRNAs in cis and trans form. Further analysis and integration of DE lncRNA maps showed that 489 mRNAs were abnormally expressed. These mRNAs may be regulated by dysregulated cis- or trans-acting lncRNAs. Among them, 289 abnormal mRNAs may be regulated by cis-acting lncRNAs and 262 by trans-acting lncRNAs.

According to RT-qPCR results, three lncRNAs (LNC-AP000769.1-1:2, ENST00000557691, and LNC-HSFY2-10:1) were up-regulated, and four lncRNAs (LNC-MGMT-2:1, LNC-POLR3E-3:3, LNC-THRSP-6:1, and LNC-PERP-2:7) were down-regulated, which was in line with microarray results. While lnc-PXDNL-4:1 expression was down-regulated in psoriasis tissues, NON-HSAT066260 and ENST00000547006 expression levels were lower in psoriasis tissues than in normal tissues, which was inconsistent with microarray results.[59] Further research is needed to determine the functions of these lncRNAs in skin tissue, particularly in psoriasis patients.

Using RNA sequencing data produced from 99 psoriasis lesions, 27 non-lesion psoriasis tissues, and 90 normal skin biopsies, 2942 previously annotated new lncRNAs and 1080 expected new skin-specific lncRNAs were detected. Notably, over 40% of the new lncRNAs were differentially expressed, and the proportion of DE transcripts between protein-encoded mRNAs in psoriatic lesions and previously annotated lncRNAs was lower than that in non-lesioned or normal skin. A host of lncRNAs, especially those that were differentially expressed (lncRNAs G2608, G25746, and G36220), were co-expressed with genes involved in immune-related functions, which increased their abundance in the epidermal differentiation complex. Moreover, different tissue-specific expression patterns and epigenetic characteristics of the new lncRNAs were identified, some of which (e.g., G26054, G26445, G2579, G6839, etc) have been shown to be affected by cytokines (IL-17).[12]

DE lncRNAs, miRNAs, and mRNAs were screened by analyzing data of accession numbers GSE54456 and GSE74697. Accordingly, a psoriasis-related lncRNA-miRNA-mRNA network based on the ceRNA theory was proposed. In addition, systematic literature searches using the PubMed and Web of Science databases helped identify miRNAs that had previously been confirmed to be abnormally expressed during psoriasis, and a specific lncRNA-miRNA-mRNA sub-network related to miRNA was produced. Moreover, gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes enrichment analyses suggested that 253 lncRNAs, 106 mRNAs, and 1156 mRNAs were differentially expressed in the skin of psoriasis patients and healthy controls. In the down-regulated lncRNA-mediated ceRNA network, only two lncRNAs, AL035425.3 and Prader-Willi/Angelman region RNA 6 (PWAR6) interacted with more than five miRNAs, suggesting that these lncRNAs may play a role in the mechanism underlying psoriasis.[60]

In a different study, RNA sequencing of psoriasis patients and healthy subjects showed that 5328 genes were differentially expressed.[62] Differential expression analysis of psoriasis patients before and after treatment revealed 2657 DEGs. Furthermore, four DE lncRNAs were selected to examine their effects, and TRHDE-AS1, CYP4Z2P, and HINT1 were differentially expressed, in line with the RNA sequencing results. The top-three GO terms of psoriasis patients and healthy subjects were genes of virus reproduction, nuclear division, and mitosis, all of which were significantly up-regulated. In psoriasis patients, the top-three GO terms were mitotic, nuclear division, and viral reproduction processes, all of which were markedly down-regulated. Using the WGCNA software package, 64 module-characteristic gene module eigengenes (MEs) were identified in psoriasis patients, compared to healthy subjects, and three of these MEs were significantly associated with psoriasis. Comparing untreated and treated psoriasis patients, 70 MEs were identified, six of which were strongly correlated with positive responses to biological therapy.[61] The functional role of these factors requires further validation.

Conclusions and Outlook

The pathogenesis of psoriasis is complicated and depends on numerous factors such as autoimmunity, environmental influences, and heredity. LncRNAs have attracted considerable attention as fundamental biomodulator factors. We review a series of lncRNAs, of which lncRNA-MSX2P1, MIR31HG, lncRNA-H19, lncRNA-RP6-65G23.1, PRINS, HOTAIR, HULC, and PRANCR were found to be up-regulated during psoriasis. They affect KC proliferation and apoptosis and induce production of inflammatory factors. Similarly, expression of AF005081, UC003af, and BC020554 increased; however, their specific functions require further examination. MEG3

and LINC00941 were down-regulated during psoriasis. In addition, lncRNA FLICR inhibits Treg cell activity by down-regulating Foxp3 expression. LncRNA MALAT1 is associated with tolerance functions of DCs and induction of immune tolerance. Many studies suggested that lncRNAs such as PSORS1C3, ANRIL, CARD14, LNC-AP000769.1-1:2, ENST00000557691, LNC-HSFY2-10:1, LNC-MGMT-2:1, LNC-POLR3E-3:3, LNC-THRSP-6:1, LNC-PERP-2:7, AL035425.3, and PWAR6 are potential biomarkers of psoriasis through RNA sequencing and microarray analysis, which, however, requires experimental verification.

Several potential applications of lncRNAs in clinical diagnosis and treatment have been suggested recently, and a growing body of evidence confirms that lncRNAs are involved in skin development, hair growth, and wound healing, with the underlying mechanism likely based on microRNA regulation. LncRNA H19 was reported to accelerate cell proliferation, extracellular matrix remodeling, and wound healing in diabetic foot ulcer through elevation of connective tissue growth factor and activation of the MAPK signaling pathway.[62] A recent study revealed that lncRNA cancer susceptibility candidate 15, an independent indicator of disease prognosis, is up-regulated during melanoma progression and participates in distant metastasis of melanoma.[63] LncRNA SAMMSON interacts with p32, the main regulator of mitochondrial homeostasis and metabolism, which increases its mitochondrial targeting and carcinogenic effects, suggesting that SAMMSON targeting reduces survival rates of melanoma patients.[64] LncRNAs play an emerging role in normal and malignant hematopoiesis[65]; moreover, epigallocatechin gallate was found to improve the cholesterol metabolism and to change expression profiles of intracellular lncRNAs in HepG2 cells, suggesting that lncRNAs may play a crucial role in cholesterol metabolism.[66] In addition, lncRNAs modulate fibroblast-like synoviocytes, differentiation of T lymphocytes and macrophages, and affect bone formation and balance of chondrocytes.[67] Although numerous functions of lncRNAs have been studied, many challenges remain to be addressed. For example, abnormal expression of lncRNAs during psoriasis and the underlying mechanisms remain unclear. Furthermore, functional differences between lncRNAs and other epigenetic factors and whether changes in lncRNAs play a causal role in disease progression require clarification.

Taken together, lncRNAs play a vital regulatory role during psoriasis. Identifying disease-related lncRNAs in psoriasis patients may help establish new biomarker systems and find potential therapeutic targets. Studying the role of lncRNAs in psoriasis occurrence and development may thus be crucial for future in-depth psoriasis research.

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Conflicts of interest

None.

References

1. Derek H, Eugene K, Andrew M, Jared J. A systematic review of light emitting diode (LED) phototherapy for treatment of psoriasis: an emerging therapeutic modality. J Drugs Dermatol 2017;16:482–488.
2. Steven RF, Haijun T, Isabelle G, Patrick M, Meng S. Economic burden of comorbidities in psoriasis patients in the United States: results from a retrospective U.S. database. BMC Health Serv Res 2017;17:337. doi: 10.1186/s12913-017-2278-0.
3. Li X, Miao X, Wang H, Wang Y, Li F, Yang Q, *et al*. Association of serum uric acid levels in psoriasis: a systematic review and meta-analysis. Medicine 2016;95:e3676. doi: 10.1097/MD.0000000000003676.
4. Li X, Kong LJ, Li FL, Chen C, Xu R, Wang HS, *et al*. Association between psoriasis and chronic obstructive pulmonary disease: a systematic review and meta-analysis. PloS One 2015;10:e0145221. doi: 10.1371/journal.pone.0145221.
5. Mitchell G, John LR. Modular regulatory principles of large non-coding RNAs. Nature 2012;482:339–346. doi: 10.1038/nature10887.
6. Liu YC, Zhao J, Zhang WH, Gan J, Hu CG, Huang GJ, *et al*. lncRNA GAS5 enhances G1 cell cycle arrest via binding to YBX1 to regulate p21 expression in stomach cancer. Sci Rep 2015;5:10159. doi: 10.1038/srep10159.
7. Wang DZ, Chen GY, Li YF, Zhang NW. Comprehensive analysis of long non-coding RNA and mRNA expression profile in rectal cancer. Chin Med J 2020;133:1312–1321. doi: 10.1097/CM9.0000000000000753.
8. Wu Y, Wang HL. Immunological mechanisms and therapeutic targets of psoriasis (in Chinese). Chin J Immun 2019;35:1281–1288. doi: 10.3969 /j.issn.1000-484X.2019.11.001.
9. Swindell WR, Sarkar MK, Liang Y, Xing X, Gudjonsson JE. Cross-disease transcriptomics: unique IL-17A signaling in psoriasis lesions and an autoimmune PBMC signature. J Invest Dermatol 2016;136:1820–1830. doi: 10.1016/j.jid.2016.04.035.
10. Lou FZ, Sun Y, Xu ZY, Niu L, Wang Z, Deng S, *et al*. Excessive polyamine generation in keratinocytes promotes self-RNA sensing by dendritic cells in psoriasis. Immunity 2020;53:204–216.e10. doi: 10.1016/j.immuni.2020.06.004.
11. Qiao M, Li R, Zhao XT, Yan JJ, Sun Q. Up-regulated lncRNA-MSX2P1 promotes the growth of IL-22-stimulated keratinocytes by inhibiting miR-6731-5p and activating S100A7. Exp Cell Res 2018;363:243–254. doi: 10.1016/j.yexcr.2018.01.014.
12. Tsoi LC, Iyer MK, Stuart PE, Swindell WR, Gudjonsson JE, Tejasvi T, *et al*. Analysis of long non-coding RNAs highlights tissue-specific expression patterns and epigenetic profiles in normal and psoriatic skin. Genome Biol 2015;16:24. doi: 10.1186/s13059-014-0570-4.
13. Szegedi K, Sonkoly E, Nagy N, Németh IB, Bata-Csörgo Z, Kemény L, *et al*. The anti-apoptotic protein G1P3 is overexpressed in psoriasis and regulated by the non-coding RNA, PRINS. Exp Dermatol 2010;19:269–278. doi: 10.1111/j.1600-0625.2010.01066.x.
14. Jia HY, Zhang K, Lu WJ, Xu GW, Zhang JF, Tang ZL. LncRNA MEG3 influences the proliferation and apoptosis of psoriasis epidermal cells by targeting miR-21/caspase-8. BMC Mol Cell Biol 2019;20:46. doi: 10.1186/s12860-019-0229-9.
15. Gao JT, Chen FR, Hua MC, Guo JF, Nong YJ, Tang QY, *et al*. Knockdown of lncRNA MIR31HG inhibits cell proliferation in human HaCaT keratinocytes. Biol Res 2018;51:30. doi: 10.1186/s40659-018-0181-8.
16. Li CX, Li HG, Huang LT, Kong YW, Chen FY, Liang JY, *et al*. H19 lncRNA regulates keratinocyte differentiation by targeting miR-130b-3p. Cell Death Dis 2017;8:e3174. doi: 10.1038/cddis.2017.516.

17. Duan QQ, Wang GR, Wang M, Chen CF, Zhang MD, Liu M, *et al*. LncRNA RP6-65G23.1 accelerates proliferation and inhibits apoptosis via p-ERK1/2/p-AKT signaling pathway on keratinocytes. J Cell Biochem 2020;121:4580–4589. doi: 10.1002/jcb.29685.
18. Bari L, Bacsa S, Sonkoly E, Bata-Csörgo Z, Kemény L, Dobozy A, *et al*. Comparison of stress-induced PRINS gene expression in normal human keratinocytes and HaCaT cells. Arch Dermatol Res 2011;303:745–752. doi: 10.1007/s00403-011-1162-8.
19. Wu MH, Chang JH, Yung BYM. Resistance to UV-induced cell-killing in nucleophosmin/B23 over-expressed NIH 3T3 fibroblasts: enhancement of DNA repair and up-regulation of PCNA in association with nucleophosmin/B23 over-expression. Carcinogenesis 2002;23:93–100. doi: 10.1093/carcin/23.1.93.
20. Kurki S, Peltonen K, Latonen L, Kiviharju TM, Ojala PM, Meek D, *et al*. Nucleolar protein NPM interacts with HDM2 and protects tumor suppressor protein p53 from HDM2-mediated degradation. Cancer Cell 2004;5:465–475. doi: 10.1016/s1535-6108(04)00110-2.
21. Szegedi K, Göblös A, Bacsa S, Antal M, Németh IB, Bata-Csörg Z, *et al*. Expression and functional studies on the noncoding RNA, PRINS. Int J Mol Sci 2012;14:205–225. doi: 10.3390/ijms14010205.
22. Liu G, Zhang WH. Long non-coding RNA HOTAIR promotes UVB-induced apoptosis and inflammatory injury by up-regulation of PKR in keratinocytes. Braz J Med Biol Res 2018;51:e6896. doi: 10.1590/1414-431X20186896.
23. Cui M, Xiao ZL, Wang Y, Zheng MY, Song TQ, Cai XL, *et al*. Long noncoding RNA HULC modulates abnormal lipid metabolism in hepatoma cells through an miR-9-mediated RXRA signaling pathway. Cancer Res 2015;75:846–857. doi: 10.1158/0008-5472.CAN-14-1192.
24. Zhao L, Man YG, Liu SM. Long non-coding RNA HULC promotes UVB-induced injury by up-regulation of BNIP3 in keratinocytes. Biomed Pharmacother 2018;104:672–678. doi: 10.1016/j.biopha.2018.05.100.
25. Quaas M, Müller GA, Engeland K. p53 can repress transcription of cell cycle genes through a p21(WAF1/CIP1)-dependent switch from MMB to DREAM protein complex binding at CHR promoter elements. Cell Cycle 2012;11:4661–4672. doi: 10.4161/cc.22917.
26. Cai P, Otten ABC, Cheng B, Ishii MA, Zhang W, Huang B, *et al*. A genome-wide long noncoding RNA CRISPRi screen identifies PRANCR as a novel regulator of epidermal homeostasis. Genome Res 2020;30:22–34. doi: 10.1101/gr.251561.119.
27. Ziegler C, Graf J, Faderl S, Schedlbauer J, Strieder N, Förstl B, *et al*. The long non-coding RNA LINC00941 and SPRR5 are novel regulators of human epidermal homeostasis. EMBO Rep 2019;20:e46612. doi: 10.15252/embr.201846612.
28. Mazar J, Sinha S, Dinger ME, Mattick JS, Perera RJ. Protein-coding and non-coding gene expression analysis in differentiating human keratinocytes using a three-dimensional epidermal equivalent. Mol Genet Genomics 2010;284:1–9. doi: 10.1007/s00438-010-0543-6.
29. Deng Y, Chang C, Lu Q. The inflammatory response in psoriasis: a comprehensive review. Clin Rev Allergy Immunol 2016;50:377–389. doi: 10.1007/s12016-016-8535-x.
30. Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, *et al*. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol 2014;133:1032–1040. doi: 10.1016/j.jaci.2014.01.025.
31. Kopp T, Riedl E, Bangert C, Bowman EP, Greisenegger E, Horowitz A, *et al*. Clinical improvement in psoriasis with specific targeting of interleukin-23. Nature 2015;521:222–226. doi: 10.1038/nature14175.
32. Guenova E, Skabytska Y, Hoetzenecker W, Weindl G, Sauer K, Tham M, *et al*. IL-4 abrogates T(H)17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells. Proc Natl Acad Sci U S A 2015;112:2163–2168. doi: 10.1073/pnas.1416922112.
33. Lai Y, Li D, Li C, Muehleisen B, Radek KA, Park HJ, *et al*. The antimicrobial protein REG3A regulates keratinocyte proliferation and differentiation after skin injury. Immunity 2012;37:74–84. doi: 10.1016/j.immuni.2012.04.010.
34. Piaserico S, Sandini E, Saldan A, Abate D. Effects of TNF-alpha inhibitors on circulating Th17 cells in patients affected by severe psoriasis. Drug Dev Res 2014;75 (Suppl 1):S73–S76. doi: 10.1002/ddr.21202.
35. Richetta AG, Mattozzi C, Salvi M, Giancristoforo S, D'epiro S, Milana B, *et al*. CD4+ CD25+ T-regulatory cells in psoriasis. Correlation between their numbers and biologics-induced clinical improvement. Eur J Dermatol 2011;21:344–348. doi: 10.1684/ejd.2011.1362.
36. Chen Z, Shi Y. 406 IL-21 regulates the balance of Th17 and Treg in psoriasis. J Invest Dermatol 2018;138:S69. doi: 10.1016/j.jid.2018.03.413.
37. Sonkoly E, Bata-Csorgo Z, Pivarcsi A, Polyanka H, Anna Kenderessy-Szabo A, Molnar G, *et al*. Identification and characterization of a novel, psoriasis susceptibility-related noncoding RNA gene, PRINS. J Biol Chem 2005;280:24159–24167. doi: 10.1074/jbc.M501704200.
38. Zemmour D, Pratama A, Loughhead SM, Mathis D, Benoist C. Flicr, a long noncoding RNA, modulates Foxp3 expression and autoimmunity. Proc Natl Acad Sci U S A 2017;114:E3472–E3480. doi: 10.1073/pnas.1700946114.
39. Schmidl C, Hansmann L, Lassmann T, Balwierz PJ, Kawaji H, Itoh M, *et al*. The enhancer and promoter landscape of human regulatory and conventional T-cell subpopulations. Blood 2014;123:68–78. doi: 10.1182/blood-2013-02-486944.
40. Chamian F, Krueger JG. Psoriasis vulgaris: an interplay of T lymphocytes, dendritic cells, and inflammatory cytokines in pathogenesis. Curr Opin Rheumatol 2004;16:331–337. doi: 10.1097/01.bor.0000129715.35024.50.
41. Gudjonsson JE, Johnston A, Sigmundsdottir H, Valdimarsson H. Immunopathogenic mechanisms in psoriasis. Clin Exp Immunol 2004;135:1–8. doi: 10.1111/j.1365-2249.2004.02310.x.
42. Yoshimoto R, Mayeda A, Yoshida M, Nakagawa S. MALAT1 long non-coding RNA in cancer. Biochim Biophys Acta 2016;1859:192–199. doi: 10.1016/j.bbagrm.2015.09.012.
43. Zhao G, Su Z, Song D, Mao Y, Mao X. The long noncoding RNA MALAT1 regulates the lipopolysaccharide-induced inflammatory response through its interaction with NF-κB. FEBS Lett 2016;590:2884–2895. doi: 10.1002/1873-3468.12315.
44. Martinez-Nunez RT, Louafi F, Friedmann PS, Sanchez-Elsner T. MicroRNA-155 modulates the pathogen binding ability of dendritic cells (DCs) by down-regulation of DC-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN). J Biol Chem 2009;284:16334–16342. doi: 10.1074/jbc.M109.011601.
45. Wu J, Zhang H, Zheng Y, Jin X, Liu M, Li S, *et al*. The long noncoding RNA MALAT1 induces tolerogenic dendritic cells and regulatory T cells via miR155/dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin/IL10 axis. Front Immunol 2018;9:1847. doi: 10.3389/fimmu.2018.01847.
46. Holm SJ, Sánchez F, Carlén LM, Mallbris L, Ståhle M, O'Brien KP. HLA-Cw*0602 associates more strongly to psoriasis in the Swedish population than variants of the novel 6p21.3 gene PSORS1C3. Acta Derm Venereol 2005;85:2–8. doi: 10.1080/00015550410023527.
47. Bochenek G, Häsler R, El Mokhtari NE, König IR, Loos BG, Jepsen S, *et al*. The large non-coding RNA ANRIL, which is associated with atherosclerosis, periodontitis and several forms of cancer, regulates ADIPOR1, VAMP3 and C11ORF10. Hum Mol Genet 2013;22:4516–4527. doi: 10.1093/hmg/ddt299.
48. Schaefer AS, Richter GM, Groessner-Schreiber B, Noack B, Nothnagel M, El Mokhtari NE, *et al*. Identification of a shared genetic susceptibility locus for coronary heart disease and periodontitis. PLoS Genet 2009;5:e1000378. doi: 10.1371/journal.pgen.1000378.
49. Zhao W, Smith JA, Mao G, Fornage M, Peyser PA, Sun YV, *et al*. The cis and trans effects of the risk variants of coronary artery disease in the Chr9p21 region. BMC Med Genomics 2015;8:21. doi: 10.1186/s12920-015-0094-0.
50. Huang X, Zhang W, Shao Z. Association between long non-coding RNA polymorphisms and cancer risk: a meta-analysis. Biosci Rep 2018;38:BSR20180365. doi: 10.1042/BSR20180365.
51. Jarinova O, Stewart AF, Roberts R, Wells G, Lau P, Naing T, *et al*. Functional analysis of the chromosome 9p21.3 coronary artery disease risk locus. Arterioscler Thromb Vasc Biol 2009;29:1671–1677. doi: 10.1161/ATVBAHA.109.189522.
52. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Mohlke KL, *et al*. INK4/ARF transcript expression is associated with chromosome 9p21 variants linked to atherosclerosis. PLoS One 2009;4:e5027. doi: 10.1371/journal.pone.0005027.
53. Rezazadeh M, Gharesouran J, Moradi M, Noroozi R, Omrani MD, Taheri M, *et al*. Association study of ANRIL genetic variants and multiple sclerosis. J Mol Neurosci 2018;65:54–59. doi: 10.1007/s12031-018-1069-3.
54. Rakhshan A, Zarrinpour N, Moradi A, Ahadi M, Omrani MD, Ghafouri-Fard S, *et al*. Genetic variants within ANRIL (antisense non

coding RNA in the INK4 locus) are associated with risk of psoriasis. Int Immunopharmacol 2020;78:106053. doi: 10.1016/j.intimp.2019.106053.
55. Hangauer MJ, Vaughn IW, McManus MT. Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs. PLoS Genet 2013;9:e1003569. doi: 10.1371/journal.pgen.1003569.
56. Li B, Tsoi LC, Swindell WR, Gudjonsson JE, Tejasvi T, Johnston A, *et al*. Transcriptome analysis of psoriasis in a large case-control sample: RNA-seq provides insights into disease mechanisms. J Invest Dermatol 2014;134:1828–1838. doi: 10.1038/jid.2014.28.
57. Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, *et al*. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. Nature Genetics 2012;44:1341–1348. doi: 10.1038/ng.2467.
58. Gupta R, Ahn R, Lai K, Mullins E, Debbaneh M, Dimon M, *et al*. Landscape of long noncoding RNAs in psoriatic and healthy skin. J Invest Dermatol 2016;136:603–609. doi: 10.1016/j.jid.2015.12.009.
59. Yan JJ, Song J, Qiao M, Zhao XT, Li RH, Jiao J, *et al*. Long noncoding RNA expression profile and functional analysis in psoriasis. Mol Med Rep 2019;19:3421–3430. doi: 10.3892/mmr.2019.9993.
60. Zhou QQ, Yu Q, Gong Y, Liu ZC, Xu H, Wang Y, *et al*. Construction of a lncRNA-miRNA-mRNA network to determine the regulatory roles of lncRNAs in psoriasis. Exp Ther Med 2019;18:4011–4021. doi: 10.3892/etm.2019.8035.
61. Ahn R, Gupta R, Lai K, Chopra N, Arron ST, Liao W. Network analysis of psoriasis reveals biological pathways and roles for coding and long non-coding RNAs. BMC Genomics 2016;17:841. doi: 10.1186/s12864-016-3188-y.
62. Li B, Zhou Y, Chen J, Wang T, Li Z, Fu Y, *et al*. Long non-coding RNA H19 contributes to wound healing of diabetic foot ulcer. J Mol Endocrinol 2020;65:69–84. doi: 10.1530/JME-19-0242.
63. Lessard L, Liu M, Marzese DM, Wang H, Chong K, Kawas N, *et al*. The CASC15 long intergenic noncoding RNA locus is involved in melanoma progression and phenotype switching. J Invest Dermatol 2015;135:2464–2474. doi: 10.1038/jid.2015.200.
64. Leucci E, Vendramin R, Spinazzi M, Laurette P, Fiers M, Wouters J, *et al*. Melanoma addiction to the long non-coding RNA SAMMSON. Nature 2016;531:518–522. doi: 10.1038/nature17161.
65. Wang FY, Gu ZY, Gao CJ. Emerging role of long non-coding RNAs in normal and malignant hematopoiesis. Chin Med J 2020;133:462–473. doi: 10.1097/CM9.0000000000000624.
66. Liu G, Zheng X, Xu Y, Lu J, Chen J, Huang X. Long non-coding RNAs expression profile in HepG2 cells reveals the potential role of long non-coding RNAs in the cholesterol metabolism. Chin Med J 2015;128:91–97. doi: 10.4103/0366-6999.147824.
67. Lao MX, Xu HS. Involvement of long non-coding RNAs in the pathogenesis of rheumatoid arthritis. Chin Med J 2020;133:941–950. doi: 10.1097/CM9.0000000000000755.

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