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REVIEW

Targeted siRNA Therapy for Psoriasis: Translating Preclinical Potential into Clinical Treatments

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Abstract: Psoriasis is a chronic inflammatory skin disease characterized by the excessive proliferation of keratinocytes and heightened immune activation. Targeting pathogenic genes through small interfering RNA (siRNA) therapy represents a promising strategy for the treatment of psoriasis. This mini-review provides a comprehensive summary of siRNA research targeting the pathogenesis of psoriasis, covering aspects such as keratinocyte function, inflammatory cell roles, preclinical animal studies, and siRNA delivery mechanisms. It details recent advancements in RNA interference that modulate key factors including keratinocyte proliferation (Fibroblast Growth Factor Receptor 2, *FGFR2*), apoptosis (Interferon Alpha Inducible Protein 6, *G1P3*), differentiation (Grainyhead Like Transcription Factor 2, *GRHL2*), and angiogenesis (Vascular Endothelial Growth Factor, *VEGF*); immune cell infiltration and inflammation (Tumor Necrosis Factor-Alpha, *TNF-α*; Interleukin-17, *IL-17*); and signaling pathways (*JAK-STAT*, Nuclear Factor Kappa B, *NF-κB*) that govern immunopathology. Despite significant advances in siRNA-targeted treatments for psoriasis, several challenges persist. Continued scientific developments promise the creation of more effective and safer siRNA medications, potentially enhancing the quality of life for psoriasis patients and revolutionizing treatments for other diseases. This article focuses on the most recent research advancements in targeting the pathogenesis of psoriasis with siRNA and explores its future therapeutic prospects.

Keywords: psoriasis, siRNA, keratinocytes, targeted delivery

Introduction

Psoriasis is a chronic, non-infectious, and disabling disease, with a global prevalence of approximately 2–3% and an increasing incidence over recent years.[1,2] It affects both genders equally, with an average age of onset at 33 years, though it generally occurs earlier in females.[3] Characterized by the excessive proliferation and abnormal differentiation of keratinocytes, along with immune cell infiltration into the epidermis and dermis, this abnormal immune activation leads to the development of raised, scaly, and erythematous skin patches. The pathogenesis of psoriasis remains complex and not yet fully elucidated. Currently, topical and systemic treatments represent the first-line therapeutic approaches for psoriasis. Topical treatments, typically used in the early stages, involve the administration of vitamin D3 or corticosteroids, supplemented by phototherapy.[4] Systemic treatments primarily comprise immunosuppressants, non-specific anti-inflammatory drugs, and molecular targeted therapies. In particular, the introduction of biologics targeting key inflammatory cytokines such as Tumor Necrosis Factor-Alpha (*TNF-α*) and Interleukin-17 (*IL-17*) has revolutionized the treatment of moderate to severe psoriasis over the past decade.[5] Compared to early-stage treatments, systemic therapies are costlier and may increase the risk of infections.[6,7] The introduction of biologic therapies has markedly improved the

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treatment of moderate to severe psoriasis. Methods of administration have evolved from subcutaneous delivery to include oral and topical medications. For instance, Tapinarof (an AhR modulator) and Roflumilast (a PDE-4 inhibitor) have demonstrated favorable efficacy and safety outcomes, leading to their approval by the FDA for the topical treatment of plaque psoriasis.[8] Psoriasis still presents many unresolved issues, notably adverse drug reactions and disease recurrence after medication discontinuation. Novel therapies may offer a promising strategy for managing these challenges and maintaining treatment efficacy.

Recently, RNA interference (RNAi) has emerged as a promising therapeutic strategy, potentially offering distinct advantages over existing systemic treatments for psoriasis. RNAi is an endogenous cellular pathway through which small double-stranded RNA molecules, known as small interfering RNAs (siRNAs), induce sequence-specific post-transcriptional gene silencing. siRNAs, which are small double-stranded RNA molecules, silence genes by interrupting the translation of DNA into proteins, thereby selectively interfering with the expression of specific genes.[9] This process can selectively target and knock out almost any gene. Consequently, siRNA therapy possesses the potential for precise and effective suppression of specific targets crucial to the pathogenesis of psoriasis. The successful application of Onpattro (Patisiran), the first RNAi therapeutic drug approved by the FDA, is viewed as an acknowledgment of the immense potential of siRNA in treating numerous diseases.[10] In December 2021, the FDA approved inclisiran for the treatment of arteriosclerotic cardiovascular disease (ASCVD), characterized by elevated LDL-C levels or heterozygous familial hypercholesterolemia (HeFH). Research has confirmed that inclisiran effectively reduces LDL-C levels in patients for whom statin therapy alone is inadequate.[11] Furthermore, the development of efficient siRNA delivery systems, such as siRNA nanocarriers, in clinical trials has significantly advanced siRNA therapy.[12] This mini-review summarizes the latest advances and explores future prospects for understanding and treating psoriasis at the molecular level through RNAi technology. Specifically, it focuses on the key studies utilizing siRNA to target and silence key mediators of excessive proliferation in keratinocytes, inflammatory immune responses, cell signaling pathways, and the differentiation processes known to drive psoriasis formation. To date, no clinical trial reports on the treatment of psoriasis with siRNA have been identified. The available research is limited to in vitro cellular experiments (involving lesional and non-lesional skin tissues from psoriasis patients as well as normal skin tissues from healthy individuals) and animal studies (such as imiquimod-induced psoriasis in mice). Consequently, this article systematically summarizes the therapeutic prospects and challenges of siRNA in treating psoriasis, aiming to provide a theoretical reference for translating preclinical siRNA results into clinical therapies.

Methods

The application of siRNAs has expanded significantly with advancing research into their physiological effects and mechanisms of action. This paper presents a comprehensive review to summarize and evaluate the potential of siRNAs in the treatment of psoriasis. For this review, two researchers independently conducted a systematic search in the PubMed database. The search was conducted using “siRNA” and “Psoriasis” as keywords, with the deadline set for November 2023. The search engine for this study retrieved a total of 158 publications; 21 were excluded after reviewing their titles, which included unrelated reviews and titles not pertinent to the study’s subject. One hundred thirty-seven documents were retained and analyzed for their abstracts and full texts; 62 were subsequently excluded due to irrelevance or incomplete information. Ultimately, 75 articles were included for analysis.

Targeting Keratinocytes

The pathogenesis of psoriasis is complex, involving intricate interactions among keratinocytes, immune cells, and other resident skin cells. It is characterized by the abnormal proliferation and differentiation of keratinocytes, alongside excessive infiltration of immune cells into the dermis and epidermis.[13] siRNA technology can inhibit the progression of psoriasis by targeting the proliferation, differentiation, apoptosis, and migration of keratinocytes.

Mediating the Proliferation and Apoptosis of Keratinocytes

The pathogenesis of psoriasis is complex, primarily due to the imbalance between the proliferation and apoptosis of keratinocytes. Abnormal proliferation of keratinocytes results in excessive cell accumulation on the skin surface, forming

characteristic psoriatic lesions. Concurrently, aberrant apoptosis contributes further to this accumulation, exacerbating psoriasis symptoms.

Firstly, siRNA-mediated gene silencing exerts specific effects on the proliferation and apoptosis of keratinocytes. For instance, siRNA silencing of Fibroblast Growth Factor Receptor 2 (*FGFR2*) inhibits keratinocyte proliferation.[14] Similarly, knockdown of Nuclear Factor of Activated T Cells 2 (*NFAT2*) reduces keratinocyte proliferation and decreases epidermal thickness.[15] Additionally, TRAF3 Interacting Protein 2 (*TRAF3IP2*) knockdown diminishes the proliferation of keratinocytes and endothelial cells by promoting apoptotic signaling and blocking the G2/M cell cycle phase.[16] Knockdown of Interferon Alpha Inducible Protein 6 (*G1P3*) via siRNA promotes apoptosis.[17] Further, siRNA knockdown experiments have confirmed the role of Aldo-Keto Reductase Family 1 Member B10 (*AKR1B10*) in promoting excessive proliferation of keratinocytes.[18] siRNA silencing of Proteasome Maturation Protein (*POMP*) inhibits keratinocyte proliferation and induces apoptosis by disrupting proteasome assembly.[19] Circ-Insulin Like Growth Factor 1 Receptor (*circIGF1R*) silencing, through regulation of the MicroRNA-194-5p/Cyclin Dependent Kinase 1 (*CDK1*) axis, inhibits keratinocyte proliferation, migration, and invasion, and induces apoptosis.[20] Knockdown of Pituitary Tumor-Transforming 2 (*PTTG2*) leads to the downregulation of vimentin and upregulation of E-cadherin, thereby enhancing the vitality and migration of keratinocytes.[21] siRNA silencing of MIR31 Host Gene (*MIR31HG*) induces cell cycle arrest at the G2/M phase and inhibits proliferation.[22] Additionally, certain siRNA-mediated gene knockdowns exhibit inhibitory effects on cell proliferation under specific conditions. For example, siRNA-mediated inhibition of Karyopherin Subunit Alpha (*KPNA*) is crucial for significantly suppressing keratinocyte proliferation under starvation conditions.[23]

Secondly, beyond individual gene siRNA silencing, analysis across multiple studies suggests that some genes exhibit inter-regulatory relationships. WT1 Associated Protein (*WTAP*) is linked to WT1 Transcription Factor (*WT1*), with both showing close functional and expression relationships. Low expression of *WT1* inhibits keratinocyte proliferation and promotes apoptosis, whereas its overexpression has the opposite effects.[24] Similarly, overexpression of *WTAP* enhances keratinocyte proliferation, while its inhibition reduces proliferation.[25] Therefore, *WTAP* and *WT1* may exhibit an upstream-downstream regulatory relationship, suggesting the need for further joint research. Early Growth Response 1 (*EGR1*) and Polo Like Kinase 2 (*PLK2*) are pro-proliferative factors with mutual regulation and interaction between *EGR1* and *WT1*. In both physiological and pathological processes, they collaboratively participate in cell growth, differentiation, and tumorigenesis.[26] Targeting *EGR1* and *PLK2* with specific siRNA in keratinocytes significantly reduces their expression, leading to decreased keratinocyte proliferation.[27]

Keratin 16 (*KRT16*) and Keratin 17 (*KRT17*) are members of the same keratin gene family, with several genes potentially related to both *KRT16* and *KRT17*. Both *KRT16* and *KRT17* exhibit high expression levels in keratinocytes. Silencing the *KRT16* gene inhibits keratinocyte proliferation,[28] while suppression of *KRT17* gene expression can both inhibit proliferation and induce apoptosis in these cells.[29] *NFE2L2* enhances keratinocyte proliferation by upregulating Keratin 6 (*KRT6*), *KRT16*, and *KRT17*; locally applied *NFE2L2* small interfering RNA subsequently reduces epidermal hyperplasia and decreases the expression of these keratins.[30] Fatty Acid Binding Protein 5 (*E-FABP*), highly expressed in the epidermis of psoriasis patients, shows that its significant inhibition markedly reduces cellular differentiation and upregulates psoriasis markers like *KRT16*.[31] siRNA-mediated knockdown of Enolase 1 (*ENO1*) significantly reduces both glycolysis and keratinocyte proliferation. Luo et al demonstrated the interaction between *KRT17* and *ENO1*, which promotes glycolysis and proliferation in keratinocytes.[32]

Many key pathogenic mediators of psoriasis are associated with the Janus kinase/Signal Transducer and Activator of Transcription (*JAK-STAT*) signaling pathway.[33] The *JAK-STAT* signaling pathway plays a crucial role in the transduction of cytokine and growth factor signals, regulating inflammatory responses, immune cell activation, keratinocyte proliferation, and abnormal differentiation.[34] Signal Transducer and Activator of Transcription 3 (*STAT3*) is highly expressed and activated in psoriatic keratinocytes, with its activity positively correlating with the severity of psoriasis. Silencing the *STAT3* gene in psoriatic keratinocytes using siRNA, combined with ultrasound irradiation and microbubble technology, inhibits keratinocyte growth and induces apoptosis.[35] Transfection of keratinocytes, whether treated or untreated with avidin, with siRNA targeting Signal Transducer and Activator of Transcription 1 (*STAT1*) and *STAT3*, confirmed that avidin regulates psoriatic keratinocyte proliferation via the *STAT* signaling pathway.[36] Inhibiting Casein Kinase 2 (*CK2*) suppresses both the *STAT3* and Threonine Kinase (*AKT*) signaling pathways in human keratinocytes, which inhibits

epidermal hyperplasia, abnormal differentiation, and the inflammatory response.[37] Protein interaction networks have shown a strong interaction between *Bcl-2* and *STAT3*, and further investigation of this relationship could reveal cellular regulatory mechanisms and provide new insights into the treatment of related diseases. Silencing *BCL2L1* and *IGF1R* with siRNA induces growth inhibition, apoptosis, and increased UVB sensitivity in keratinocytes.[38]

Mediating the Differentiation of Keratinocytes

In addition to excessive proliferation, abnormal differentiation of keratinocytes is a key characteristic of psoriasis.[39] Multiple studies have demonstrated that inhibiting genes regulating differentiation can shift the keratinocyte phenotype from psoriatic to normal. siRNA-mediated knockdown of Grainyhead Like Transcription Factor 2 (*GRHL2*) promotes normal differentiation in keratinocytes.[40] Silencing Sphingosine-1-Phosphate Lyase 1 (*SGPL1*) inhibits *S1P* cleavage enzymes in keratinocytes, thereby reducing cell proliferation and promoting normal differentiation.[41,42] Silencing Cathepsin B (*CTSB*) rescues both the excessive proliferation and inflammatory responses induced by *IL-17A* and Serum Amyloid A (*SAA*), and corrects the deficiency in normal differentiation.[43] Exogenous *CK2* promotes excessive proliferation and abnormal differentiation in human keratinocytes, which can be reversed by siRNA-mediated *CK2* inhibition. *CK2* downregulation reduces *IL-17A* expression and eliminates both proliferation and inflammatory cytokine expression in keratinocytes induced by *IL-17A*.[37] Furthermore, *Gasdermin D* gene knockout in mice exhibited normal keratinocyte proliferation and differentiation, and provided protection against psoriasiform inflammation. This suggests that siRNA-mediated gene silencing aimed at regulating differentiation may serve as a coordinated therapeutic approach for treating psoriasis symptoms.[44]

Inhibiting VEGF Secretion, Impeding Angiogenesis

Angiogenesis is abnormally active in psoriatic lesions and is closely related to disease progression.[45] Inflammatory cells promote endothelial cell migration, proliferation, and survival by releasing factors like Vascular Endothelial Growth Factor (*VEGF*). This activity induces angiogenesis, which in turn leads to the formation of vascular erythematous plaques, thereby exacerbating the condition.[46,47]

Aquaporin-1 (*AQP1*) functions as a water channel membrane protein. Nicchia et al employed siRNA to knock out *AQP1*, confirming its role as an angiogenic protein implicated in treating diseases related to angiogenesis, including cancer, psoriasis, endometriosis, arthritis, and atherosclerosis. The role of *AQP1* in sustaining endothelial cell activity during angiogenesis may represent a potential target for anti-angiogenic therapies.[48] Nerve Growth Factor (*NGF*) regulates *VEGF* expression in human keratinocytes via the Phosphatidylinositol-4,5-Bisphosphate 3-Kinase/Mechanistic Target of Rapamycin Kinase (*PI3K/MTOR*) signaling pathway, and siRNA-mediated silencing of Hypoxia Inducible Factor 1 Subunit Alpha (*HIF-1α*) can block the NGF-induced transcriptional increase of *VEGF*.[49] Downregulation of TRAF3 Interacting Protein 2 (*TRAF3IP2*) alters both the expression and secretion of VEGF in keratinocytes and endothelial cells.[16] KRT16 gene silencing inhibits not only keratinocyte proliferation via the Extracellular Signal-Related Kinase (*ERK*) signaling pathway but also the secretion of *VEGF* by keratinocytes.[28] EGF Like Repeats And Discoidin Domains 3 (*EDIL3*) induce angiogenesis in endothelial cells through the *αvβ3-FAK/MEK/ERK* signaling pathway.[50]

Regulating Inflammatory Cells, Reducing Inflammatory Cell Infiltration

Psoriasis is a chronic inflammatory skin disease that is closely associated with the activity of inflammatory cells. Histopathological features of psoriatic skin include excessive proliferation and abnormal differentiation of epidermal keratinocytes, which lead to epidermal thickening, accompanied by the infiltration of immune cells.[51] Extensive infiltration of lymphocytes, macrophages, and neutrophils into the skin characterizes the hallmark of psoriatic lesions.[52]

Neutrophil infiltration, a marker of psoriasis, is significantly reduced following treatment with mesenchymal stem/stromal cells (MSCs)-IT. Mesenchymal stem cells transduced with TNF Alpha Induced Protein 6 (*TSG-6*) siRNA lose their therapeutic effect; however, applying recombinant *TSG-6* alone can decrease neutrophil infiltration and alleviate psoriatic lesions. This finding confirms the potential therapeutic application of blocking neutrophil recruitment via MSCs-IT or *TSG-6* in the treatment of psoriasis.[53] Knockout of Ubiquitin Specific Peptidase 15 (*USP15*) results in

reduced inflammation in psoriatic keratinocytes, as well as impaired vitality and clonogenicity. Topical application of *USP15* small interfering RNA significantly improves imiquimod (IMQ)-induced psoriatic dermatitis by reducing the infiltration of T cells and neutrophils.[54] Experimental research on the therapeutic effects of *KRT17*-specific siRNA in IMQ-induced psoriasiform dermatitis in mice demonstrated a significant reduction in the severity of ear dermatitis, characterized by a reduced inflammatory phenotype, including decreased ear thickness and reduced infiltration of inflammatory cells (CD3+ T cells and neutrophils).[55]

Preclinical Animal Research Progress

Preclinical animal experiments are a crucial step in translating gene therapy into clinical research. Consequently, effectively silencing genes through single-gene siRNA represents an important focus for future in-depth studies. Silencing NFKB Inhibitor Zeta (*NFKBIZ*) via siRNA has revealed its role as a key regulatory factor for specific psoriasis-related genes and proteins induced by *IL-17F*.[56,57] Additionally, local intradermal injection of *NFKBIZ* siRNA to ablate NFKBIZ function can eliminate psoriasiform skin inflammation,[58] suggesting that *NFKBIZ* antagonists may offer a targeted approach for treating psoriasis. Experimental research on *KRT17*-specific siRNA in IMQ-induced psoriasiform dermatitis in mice has shown it reduces inflammatory cell infiltration and decreases expression levels of *IL-17*, *IL-22*, and *IL-23*, 55 indicating *KRT17*'s potential as a new target for future psoriasis treatments. The isoflavonoid compound Lignum vitae can alleviate psoriasiform inflammation in mice by inhibiting the *STAT3* and Nuclear Factor Kappa B (*NF-κB*) signaling pathways.[59] Fan et al demonstrated that silencing REL in mice not only prevents and improves IMQ-induced psoriasis but also significantly blocks the expression of various inflammatory cytokines.[60] Increased expression of Phospholipase A2 Group IVB (*PLA2G4B*) in the early stages of inflammation triggers the release of inflammatory factors like *IL-17* and *IL-36* by CD8+ naive and Th17 T cells, exacerbating inflammation and keratinocyte proliferation at lesion sites; however, knockdown of *PLA2G4B* improves inflammation.[61] Oxymatrine alleviates itching and inflammation in psoriasis by inhibiting Heat Shock Protein 90 (*HSP90*) and Heat Shock Protein 60 (*HSP60*) in keratinocytes via the Mitogen-Activated Protein Kinase (*MAPK*) signaling pathway.[62] In the piclidenoson-induced psoriasis mouse model, local application of Interferon Alpha Inducible Protein 27 (*IFI27*) siRNA reduces epidermal thickness, rete ridge formation, and Proliferating Cell Nuclear Antigen (*PCNA*) expression.[63]

Optimizing siRNA Delivery - Novel Drug Development

Although siRNA therapy holds great promise, delivering intact siRNA across the stratum corneum barrier poses a significant challenge for topical treatments. Advanced drug delivery systems are currently being developed to overcome these challenges and optimize local siRNA delivery for psoriasis. For instance,[9] laser-assisted siRNA delivery methods have improved in vivo psoriasiform lesion models by silencing epidermal IL-6, thereby improving psoriatic plaques; Solid silicon microneedle arrays have perforated and delivered cholesterol-modified *GAPDH* siRNA into mouse ear skin, reducing *GAPDH* expression by up to 66% without major organ accumulation. This demonstration marks the first effective, non-invasive delivery of siRNA to relevant skin areas using solid microneedle arrays;[64] Effective skin penetration of siRNA has been achieved through non-covalent complexation with hydrophobic cationic or choline-geranic acid ionic liquids (CAGE);[65] Transdermal IL platforms, utilizing ionic liquids, not only achieved significant gene ablation in an imiquimod-induced psoriasiform skin inflammation model but also permitted repeated application and scalability;[66] Furthermore, SPACE peptides combined with siRNA have enhanced both skin absorption of siRNA and the knockdown of corresponding protein targets.[67] Additionally, techniques like nanostructured lipid carriers, nanoparticles, and SECosome technology have enhanced siRNA delivery and its anti-psoriatic effects. In summary, the development of numerous siRNA delivery platforms is expected to gradually overcome penetration issues, enabling more precise and effective siRNA delivery, leading to clinical translation.

Advantages and Limitations

The advantages of siRNA therapy in treating psoriasis are becoming increasingly evident with the continuous advancement of technology. For instance, combining siRNA therapy with other treatments, such as topical medications and phototherapy, is evolving in clinical practice to enhance efficacy and reduce side effects. This novel therapeutic approach

may hold considerable potential for addressing disease relapse and maintaining treatment effects. Furthermore, the ongoing development of new delivery systems, including nanoparticles, nano-lipid carriers, and solid microneedle arrays, shows promise in potentially resolving drug delivery challenges. However, it remains an undeniable fact that the application of siRNA therapy in psoriasis treatment is still at a preliminary exploration stage. Current research is largely confined to in vitro cell studies and animal experiments, with a lack of convincing clinical trial evidence. Although most existing studies have achieved satisfactory outcomes, concerns persist that targeting gene silencing could lead to severe consequences. For example, studies have shown that a significant proportion of mice with targeted silencing of NFKBIZ did not survive,[56] highlighting potential risks associated with siRNA technology. Although optimizing delivery platforms may address drug delivery difficulties, their application in clinical trials has not yet been realized, complicating the assessment of long-term effects and risks associated with carrier materials.[68] Additionally, the cost of applying this novel treatment approach presents a significant barrier to transitioning from in vitro experiments to clinical applications.

Discussions

As a novel therapeutic approach, siRNA offers notable advantages, including high specificity and minimal side effects. It holds considerable potential in the treatment of psoriasis (Table 1). Recent studies have elucidated siRNA's pivotal role in modulating the pathogenesis of psoriasis. The application of siRNA can inhibit a range of mediators responsible for psoriasis development, including overproliferative agents, inflammatory cytokines, cellular signaling molecules, and differentiation regulators (Figure 1).

Table 1 Therapeutic Role of siRNA in Psoriasis and Its Potential Applications

Reference	Gene	Pathway	Cell	Potential Applications
[14]	FGFR2		Keratinocytes	This study implicates miR-125b as a potential therapeutic target for psoriasis
[15]	NFAT2		Keratinocytes	NFAT2 is a key regulator of keratinized cell proliferation and a potential molecular target associated with lithium-induced psoriasis
[16]	TRAF3IP2		Keratinocytes/ endothelial cells	TRAF3IP2 may be a potential therapeutic target for psoriasis
[17]	G1P3		Keratinocytes	Expression of G1P3 protein contributes to the maintenance of hyperproliferation of keratinized cells during psoriasis development and is a potential target for the treatment of psoriasis
[18]	AKR1B10		Keratinocytes	Demonstrated to induce hyperproliferation of keratinized cells by knockdown validation assays, providing a target for further therapeutic options in psoriasis
[20]	circIGF1R	miR-194-5p/ CDK1	Keratinocytes	circIGF1R may serve as a potential therapeutic target for psoriasis
[21]	PTTG2		Keratinocytes	PTTG2 might be a potential therapeutic target for psoriasis through inducing epithelial-to-mesenchymal transition (EMT) via regulating the expression of vimentin and E-cadherin.
[22]	MIR31HG	NF-κB	Keratinocytes	MIR31HG plays an important role in the regulation of keratinocyte hyperproliferation in psoriasis and may be an attractive therapeutic target
[23]	KPNA2		Keratinocytes	Clarifying the function of KPNA2 in cell proliferation will be a focal point for the development of novel therapies targeting KPNA2.
[24]	WT1		Keratinocytes	Providing a new target for psoriasis treatment

(*Continued*)

Table 1 (Continued).

Reference	Gene	Pathway	Cell	Potential Applications
[25]	WTAP		Keratinocytes	Overexpression of WTAP may contribute to the pathogenesis of psoriasis by regulating cell cycle progression, WTAP is a potential therapeutic target for psoriasis treatment.
[27]	EGR1/PLK2		Keratinocytes	The results provide a basis for the development of new compounds for the treatment of proliferative skin diseases such as psoriasis
[28]	KRT16	ERK	Keratinocytes	Silencing KRT16 inhibits keratinocyte proliferation and VEGF secretion in psoriasis via inhibition of ERK signaling pathway, which provides a basic theory in the treatment of psoriasis.
[29,55]	K17		Keratinocytes	Anti-K17 therapy is an effective treatment option for psoriasis, and the K17 molecule, as a new target, may hold tremendous potential for the treatment of psoriasis in the future.
[32]	ENO1/K17		Keratinocytes	Revealed the mechanism by which K17 interacts with ENO1 to promote glycolysis and proliferation of KCs, provides a new perspective for the study of the correlation between proliferation and metabolism.
[35,36]	STAT1/ STAT3	JAK/STAT	Keratinocytes	Silencing STAT1 and STAT3 can inhibit the proliferation of keratinocytes.
[37]	CK2	STAT3/AKT	Keratinocytes	CK2 may be a target for the treatment of psoriasis
[38]	BCL2L1/ IGF-1R		Keratinocytes	BCL2L1 and IGF-1R are important targets for the inhibition of keratinocyte hyperproliferation by siRNA technology
[40]	GRHL2		Keratinocytes	Promotion of keratinocyte differentiation by miR-217 is partially mediated by the inhibition of its direct target GRHL2. And may represent a novel therapeutic target for psoriasis treatment.
[41,42]	S1P		Keratinocytes	S1P lyase is a modulating factor for proliferation and differentiation, and support its potential as a therapeutic target for psoriasis in human keratinocytes.
[43]	Cathepsin B		Keratinocytes	Cathepsin B might be a promising therapeutic target for psoriasis-like lesion, which helps to develop an anti-psoriatic agent
[44]	Gasdermin D		Keratinocytes	Targeted focal death could be considered a therapeutic strategy for psoriasis
[48]	AQP1		Endothelial cells	The present study confirms that AQP1 is a pro-angiogenic protein and therefore may be a candidate target for anti-angiogenic molecules
[49]	HIF-1α		Keratinocytes	May provide insights into the pathophysiology of neuro inflammatory skin diseases such as psoriasis
[50]	EDIL3	αvβ3- FAK/ MEK/ERK	Endothelial cells	EDIL3 and αvβ3- FAK/MEK/ERK signaling pathways will provide valuable therapeutic targets for controlling angiogenesis
[53]	TSG-6		Neutrophils	Blocking neutrophil recruitment by MSCs-IT or TSG-6 has potential for therapeutic application in human psoriasis.
[54,69]	USP15		Keratinocytes	USP15 may be a potential target for the treatment of psoriasis
[56–58]	NFKBIZ	MAPK/ NF-κB	Keratinocytes	Future studies elucidating the regulation of IκBζ will enhance its potential as a therapeutic target in psoriasis and other inflammatory diseases
[60]	REL		T-Cells	Susceptibility gene Rel could be targeted to treat and prevent psoriasis
[61]	PLA2G4B		Keratinocytes	Phospholipase inhibition-based therapy reveals potential for anti-psoriasis drugs

(*Continued*)

Table 1 (Continued).

Reference	Gene	Pathway	Cell	Potential Applications
[62]	HSP90/60	MAPK	Keratinocytes	OMT-mediated reduction of HSP90 and HSP60 in keratinocytes of psoriasis mice further confirmed the anti-pruritic effect of OMT.
[63]	IFI27		Keratinocytes	This study demonstrates that IFI27 is required for cell proliferation in vitro and in vivo, and that if27 may be a suitable target for the development of a novel anti-psoriasis therapy
[70]	SERPINB2		Neutrophils	Since SERPINB2 expression is positively correlated with psoriasis severity, it may be used as a biomarker for psoriasis
[71]	Notch-1		Endothelial cells	The Notch-ligand receptor pathway may regulate vascular dysfunction and pro-inflammatory mechanisms involved in the pathogenesis of psoriasis, suggesting that targeted blockade of this pathway may have important therapeutic implications.
[72]	Gasdermin B		Keratinocytes	This study suggests that Gasdermin B may be associated with psoriasis
[73]	βTrCP	NF-κB	Keratinocytes	βTrCP is involved in the NF-κB signaling mediated-, psoriasis-related inflammation and represent a novel target for developing agents to treat psoriasis.
[74]	bFGF	JNK/SAPK	Endothelial cells	Modulation of the JNK/SAPK signaling pathway may be a promising therapeutic approach for treating angiogenesis-related diseases
[75]	STC1		Keratinocytes	Targeting STC1 and/or signaling molecules induced by STC1 could be a new therapeutic strategy for controlling diseases involving dysregulation of epidermal and dermal interactions.
[76]	ULK1		Keratinocytes	ULK1 Inhibitors May Be a Potential Option for Treating or Preventing Psoriasis Recurrence
[77]	Tcf7l1		Keratinocytes	Targeting the Tcf7l1–LCN2 axis may be one of the approaches in managing skin diseases with dysregulated keratinocyte differentiation.
[78]	S100A7	PI3K/NF-κB	Keratinocytes/ endothelial cells	This study findings raise the possibility that psoriasin could be evaluated as a novel antiangiogenic target in psoriasis
[79]	AKT	PI3K/AKT	Keratinocytes	Survivin and the PI3K/AKT signaling pathway could be potential new targets for psoriasis therapy and may provide new ideas for psoriasis treatment
[80]	TREM-1	PI3K	Keratinocytes	This study provides important clues for understanding the potential pathogenesis mechanism of psoriasis in which HIF-1α is regulated by the TREM-1 signaling pathway

Abbreviations: FGFR2, Fibroblast Growth Factor Receptor 2; NFAT2, Nuclear Factor of Activated T Cells 2; TRAF3IP2, TRAF3 Interacting Protein 2; G1P3, Interferon Alpha Inducible Protein 6; AKR1B10, Aldo-Keto Reductase Family 1 Member B10; POMP, Proteasome Maturation Protein; circIGF1R, Circ-Insulin Like Growth Factor 1 Receptor; CDK1, Cyclin Dependent Kinase 1; PTTG2, Pituitary Tumor-Transforming 2; MIR31HG, MIR31 Host Gene; KPNA, Karyopherin Subunit Alpha; WTAP, WT1 Associated Protein; WT1, WT1 Transcription Factor; EGR1, Early Growth Response 1; PLK2, Polo Like Kinase 2; KRT16, Keratin 16; KRT17, Keratin 17; KRT6, Keratin 6; E-FABP, Fatty Acid Binding Protein 5; ENO1, Enolase 1; JAK- STAT, The Janus kinase/Signal Transducer And Activator of Transcription; STAT3, Signal Transducer And Activator of Transcription 3; STAT1, Signal Transducer And Activator of Transcription 1; CK2, Casein Kinase 2; AKT, Threonine Kinase; GRHL2, Grainyhead Like Transcription Factor 2; SGPL1, Sphingosine-1-Phosphate Lyase 1; AQP1, Aquaporin 1; VEGF, Vascular Endothelial Growth Factor; EDIL3, EGF Like Repeats And Discoidin Domains 3; NGF, Nerve Growth Factor; PI3K, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; MTOR, Mechanistic Target of Rapamycin Kinase; HIF-1α, Hypoxia Inducible Factor 1 Subunit Alpha; TRAF3IP2, TRAF3 Interacting Protein 2; ERK, Extracellular Signal-Related Kinase; TSG-6, TNF Alpha Induced Protein 6; USP15, Ubiquitin Specific Peptidase 15; NFKBIZ, NFKB Inhibitor Zeta; NF-κB, Nuclear Factor Kappa B; PLA2G4B, Phospholipase A2 Group IVB; MAPK, Mitogen-Activated Protein Kinase; HSP90, Heat Shock Protein 90; HSP60, Heat Shock Protein 60; IFI27, Interferon Alpha Inducible Protein 27; PCNA, Proliferating Cell Nuclear Antigen; SAA, Serum Amyloid A; CTSB, cathepsin B; SRF, Serum Response Factor; PC1, polycystin 1; PGRN, Granulin Precursor.

Some genes identified in studies positively affect disease progression by slowing it down and thus, cannot be targeted for gene silencing. Studies have demonstrated that Serum Response Factor (SRF) expression is strongly downregulated in the hyperproliferative epidermis of wounded and psoriatic skin. Further, siRNA-mediated knockdown of SRF in primary

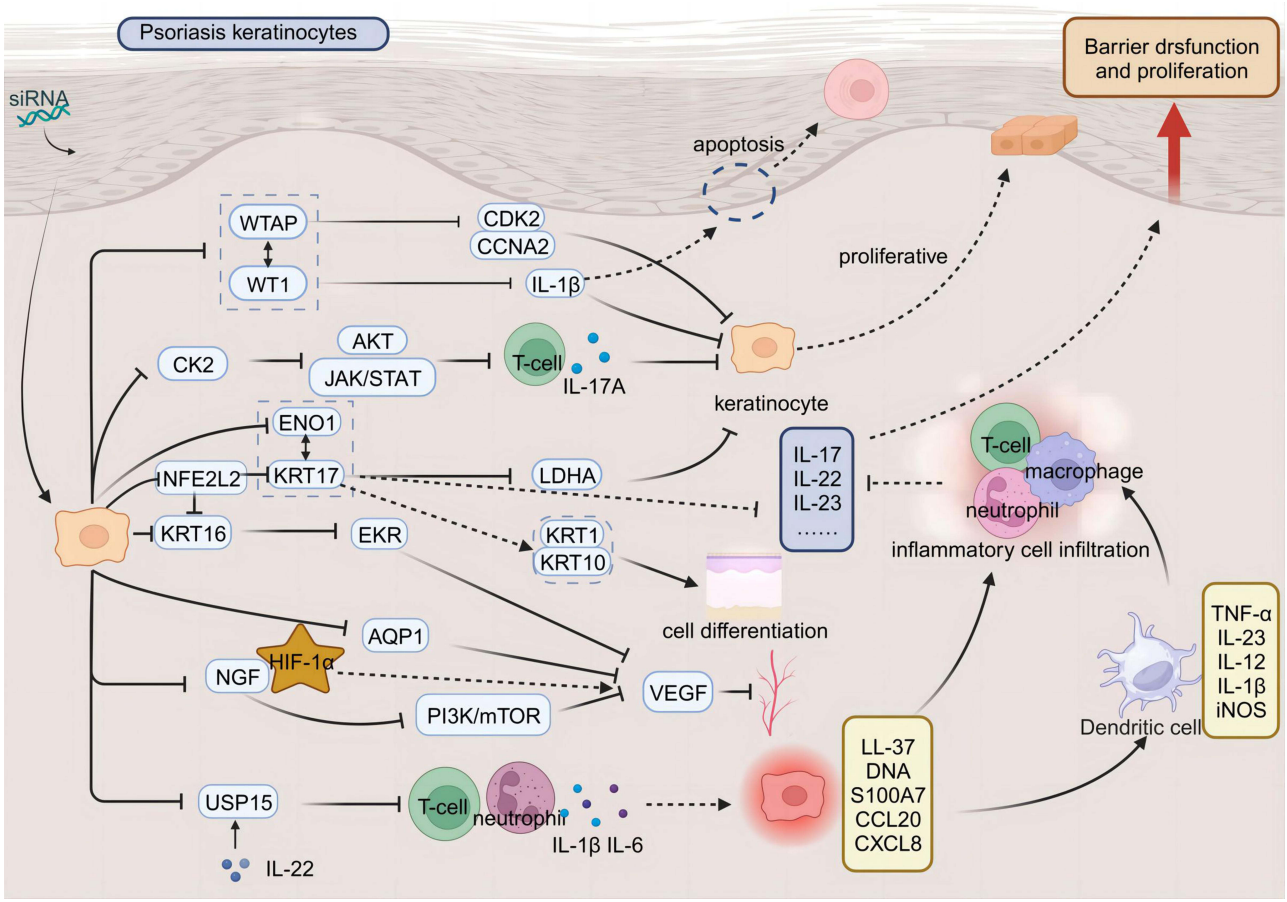

Figure 1 Therapeutic applications of siRNA in targeting pathogenic pathways underlying psoriasis. Therapeutic application of small interfering RNA (siRNA) targets the pathogenic pathways of psoriasis. In a physiological state, skin keratinocytes proliferate normally and fulfill a barrier function. In the pathological state of psoriasis, immune cells activate keratinocytes, leading to their rapid proliferation, abnormal differentiation, and inhibited apoptosis; this also promotes angiogenesis and increases inflammatory cell infiltration. Such activation disrupts the skin barrier function and causes a dysregulation in the normal proliferative capacity of keratinocytes, exacerbating the condition. siRNA therapy represents a promising strategy for treating psoriasis by silencing disease-causing genes. siRNA targets keratinocytes, silencing genes such as Casein Kinase 2 (CK2), WT1 Associated Protein (WTAP), WT1 Transcription Factor (WT1), and Enolase 1 (ENO1), which inhibits their proliferation. This action induces their normal differentiation and promotes apoptosis. Additionally, silencing genes such as Aquaporin 1 (AQP1), Nerve Growth Factor (NGF), and Keratin 16 (KRT16) inhibits Vascular Endothelial Growth Factor (VEGF), thereby hindering angiogenesis in psoriasis; Furthermore, targeting genes such as Ubiquitin Specific Peptidase 15 (USP15) and Keratin 17 (KRT17) can reduce inflammatory cell infiltration and attenuate the inflammatory response.

human keratinocytes revealed that cytoskeletal abnormalities and adhesion defects were direct consequences of SRF loss.[81] Inhibition of Polycystin 1 (PC1) function was associated with increased cell proliferation and migration in human keratinocytes.[82] Furthermore, overexpression of Granulin Precursor (PGRN) has been shown to inhibit keratinocyte inflammation by negatively regulating the production of inflammatory factors and positively influencing autophagy.[83] Therefore, the selection of genes for siRNA silencing requires further investigation.

Psoriasis is one of the autoimmune diseases that significantly affects the quality of life of patients.[84] With skin manifestations that may be associated with psoriatic arthritis, cardiovascular diseases, and inflammatory bowel disease. Therapeutic approaches should target not only psoriasis itself but also adopt a holistic perspective that includes the treatment of associated comorbidities. Given that psoriasis and certain comorbidities share similar pathogenic and inflammatory pathways or cytokines, this holistic approach has prompted experimental studies to repurpose drugs originally developed for other conditions to treat diseases with shared pathogenic mechanisms.[85] Due to variability in disease manifestation and comorbidity profiles among patients, future treatment strategies may involve selecting personalized siRNA therapies tailored to individual needs and the specific comorbidities each patient faces. This potential direction in developing novel treatment approaches underscores the importance of personalized and holistic care in managing psoriasis and its related conditions.

Conclusions

Compared to current systemic biologics, siRNA therapy may offer a more targeted approach and potentially reduce side effects. Looking forward, priority areas include evaluating the synergistic effects of siRNA combinations on interconnected molecular targets and conducting clinical trials to translate this promising preclinical research into viable psoriasis treatments. Additionally, personalizing siRNA therapy to accommodate various disease courses and types will be a key direction for future research. Furthermore, reducing the toxicity, immunogenicity, and cost of siRNA carrier materials is crucial for translating RNAi technology from preclinical research to clinical applications. With ongoing in-depth research and continuous technological innovation, siRNA is expected to become a significant tool in the treatment of psoriasis. It is also anticipated to be used in treating other diseases as delivery technologies advance and application costs decrease.

Consent to Participate

All the authors listed in this manuscript have participated in the whole writing process of the manuscript and have informed consent to the publication of the manuscript.

Consent for Publication

The research article is original, has not already been published in any other journal (medical, or otherwise) and is not currently under consideration for publication by another journal, and does not infringe any existing copyright or any other rights prescribed by law.

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.

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