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The Role of MicroRNA-21 in Psoriasis Vulgaris

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Abstract
Background: Psoriasis vulgaris is an immune-mediated skin disorder driven by miR-21–mediated survival of autoreactive T cells, pro-inflammatory STAT3 signaling, and keratinocyte hyperproliferation through suppression of regulatory genes such as PDCD4 and PTEN. MicroRNA-21 (miR-21), a 22-nucleotide non-coding RNA, is significantly overexpressed in psoriatic skin compared to healthy controls. **Objective:** To evaluate the role of miR-21 in the diagnosis, prognosis, and therapeutic monitoring of psoriasis vulgaris. **Methods:** A literature search of Medline databases (PubMed and Medscape) was conducted up to 2023. Studies were included if they were peer-reviewed, English-language articles that assessed miR-21 expression in lesional skin or blood samples (serum or plasma) of psoriasis vulgaris patients. **Study Selection:** Each study was independently reviewed. Inclusion criteria required relevant assessment of miR-21 expression and clinical correlation in psoriasis vulgaris. Studies were excluded if they lacked control groups, methodological clarity, or outcome relevance. **Data Extraction and Quality Assessment:** Data were independently extracted using a structured form. Studies were assessed for quality based on availability of controls, evaluation metrics, completeness of reporting, and ethical approval. **Results and Conclusion:** miR-21 is consistently overexpressed in psoriatic patients and correlates positively with PASI scores, supporting its role in disease severity assessment. Its modulation following treatment suggests potential as a diagnostic and prognostic biomarker and a future therapeutic target.

Keywords: Pemphigoid skin condition, microRNA-21, PASI Score.

1. Introduction

Worldwide, 2-3% of the population is affected by psoriasis, a chronic inflammatory skin condition that affects 0.5-1% of children. Evidence suggests that psoriasis is complex and involves more than one cause, including factors such as immunological dysfunction, skin barrier disturbance, environmental triggers, and genetic predisposition [1].

Worldwide, psoriasis is a significant healthcare burden due to its chronic and inflammatory components, which impact the skin and can contribute to the development of numerous comorbidities, including hypertension, dyslipidaemia, fatty liver, psychosocial conditions, and inflammatory bowel disease [2].

The development and course of psoriasis are influenced by a myriad of variables, including genetics, the immune system, and the environment. Keratinocytes and immune cells interact in a way that drastically impacts quality of life. Keratinocytes, dendritic cells, T lymphocytes, neutrophils, macrophages, natural killer cells, and mast cells are only a few of the immune cells that interact intricately to control it [3].

For its part in psoriasis's aetiology and the function it plays, epigenetics has recently been in the spotlight. MicroRNAs (miRNAs) are becoming more and more recognised as potential regulators of hyperproliferation, aberrant keratinocyte differentiation, and aberrant immune activation in psoriasis.

So, to uncover and summarize the roles of miRNAs in psoriasis, researchers are looking at the immunological activities of miRNAs and how they may be used as biomarkers in the disease's diagnosis and therapy [4].

miRNAs and miR-21

Noncoding RNAs, or miRNAs, typically consist of 19–24 nucleotides. Since 1993, the first known miRNA species, lin-4, has been found in the Caenorhabditis elegans. miRNA is an essential component of cancer biology, including cell growth, proliferation, differentiation, and apoptosis, and it functions as an endogenous regulator of gene expression [5].

When cells are under certain types of stress, they secrete miRNAs. Apoptotic bodies and exosomes, ribonucleoprotein complexes, high density lipoproteins, and microvesicles are the passive and active release mechanisms of miRNAs, respectively, that occur after cell death [6].

Because of their relative stability in the face of drastic variations in pH and temperature, as well as the simplicity with which they may be extracted from bodily fluids, they have great promise as circulating biomarkers for complicated disorders [7].

Among miRNA's many positive and negative regulatory functions are the aforementioned processes of transcript degradation, sequestering, and translation suppression. Translational and transcriptional activation are part of the negative. Because of their impact on gene regulation, they have a part in numerous biological activities. Missenses in microRNA expression had is currently being studied, and miRNA-based treatments have already been integrated into several disease conditions [8]. miRNAs are recognized for their significant involvement in regulating processes associated with psoriasis, such as hyperproliferation, epidermal keratinocyte differentiation, apoptosis, and abnormal immune activation [4]. Psoriatic skin, blood, and hair samples all show different miRNA profiles [9].

There is evidence that miR-21 reduces apoptosis in activated T cells; hence, overexpression of miR-21 may lead to T cell-derived psoriatic skin inflammation [10]. This evidence is supported by the expression of miR-21 in dermal T cells and epidermal cells in both healthy and psoriasis skin.

Patients with psoriasis show elevated levels of microRNA-21 in their skin lesions, which in turn decreases the expression of TIMP-3 in the skin and activates TACE/ADAM17, an enzyme that breaks down extracellular matrix components [11].

2. Aim of the Review

To explore the role of miR-21 in psoriasis vulgaris, focusing on its diagnostic, prognostic, and therapeutic potential. We examine how miR-21 expression differs between psoriatic and healthy individuals, its correlation with disease severity indices such as the Psoriasis Area and Severity Index (PASI), its functional involvement in key pathogenic pathways—particularly inflammation and keratinocyte regulation—and its emerging value as a therapeutic target for modulating immune responses in psoriatic skin.

Sources of Information and Study Selection

The function of miR-21 expression in the diagnosis and prognosis of psoriasis vulgaris — including its correlation with disease severity indices such as the PASI score — up till 2023 was determined by examining and analyzing Medline databases (Pub Med and Medscape).

Eligibility Criteria and Data Extraction

All studies were independently reviewed and screened according to a set of predefined inclusion and exclusion criteria. Only English-language, peer-reviewed studies that specifically investigated the role of miR-21 in the diagnosis or prognosis of psoriasis were considered eligible. Studies were excluded if they lacked relevance to miR-21 expression, provided insufficient methodological detail, did not include appropriate control groups, or failed to report psoriasis-related clinical outcomes.

Each selected study was then evaluated for methodological quality based on several key indicators: clarity and transparency of evaluation metrics, the presence and adequacy of control groups, the depth and completeness of data reporting, and the availability of documented ethical approval. Relevant data were independently extracted using a structured data collection form, ensuring consistency and focus on variables aligned with the aims of this review.

Skin Inflammation in Psoriasis

Psoriasis is a chronic immune-mediated skin disease characterized by epidermal hyperproliferation, vascular changes, and dermal leukocytic infiltration. Once considered primarily a keratinocyte disorder, current understanding highlights a complex interaction between keratinocytes and immune cells — including dendritic cells, T cells (Th1, Th17, and Th22), neutrophils, and tissue-resident memory T cells [12]. The pathogenic cascade begins with the activation of plasmacytoid and myeloid dendritic cells, which lead to the secretion of pro-inflammatory cytokines such as IFN-α, TNF-α, and IL-23. These in turn promote Th17/Th22 differentiation and the release of cytokines like IL-17A and IL-22, which drive keratinocyte proliferation and amplify inflammation. This cytokine–keratinocyte crosstalk creates a self-sustaining inflammatory loop that contributes to the severity and chronicity of the disease [13,14].

miR-21s

On average, microRNA-21s are 22 nucleotides long and are tiny non-coding RNAs. Primordiasis into precursors and maturation into miRNAs is the standard process for miRNAs, with the majority of miRNAs being transcribed from DNA sequences into pri-miRNAs. The 3′ untranslated region (UTR) of target mRNAs is the most common site for miRNAs to exert their expression-suppressing effects; nevertheless, reports of miRNA interactions with the 5′ UTR, coding sequence, and gene promoters have also been made [15].

miRNAs are often transcribed in long strands called clusters. When miRNAs in a cluster have comparable seed areas, we say that they constitute a family. Two main types of miRNA biogenesis pathways are recognised: canonical and non-canonical [16].

Overexpression of microRNA-21, one of the first oncogenic miRNAs (oncomiRs), is seen in the vast majority of malignancies. Many of these malignancies may be detectable or predictive of prognosis by measuring circulating miR-21. Overexpression of microRNA-21 is linked to cancer cells' resistance to drugs [17].

There has been a lot of research on the role of miR-21 because of its relevance to cancer and other disorders. We know that miR-21 directly targets many proteins, such as PDCD4, PTEN, SPRY1, and PPARα, which stand for peroxisome proliferator-activated receptor α. One potential mechanism by which miR-21 inhibits the tumour suppressor and apoptotic factor PDCD4 is via the development and spread of cancer. Increased cancer cell proliferation and motility have been associated with down-regulating PTEN, which has also been identified as a miR-21 target in cancer [18].

While miR-21 was originally connected with cancer, new research has linked it to a variety of pathological processes, such as cardiovascular disease, renal fibrosis, and wound healing [19].

Overexpression of miR-21 reduces cardiac contractility, and its expression rises in cardiac fibroblasts along the course of cardiac illness. The disruption of organ structure and the progression of renal fibrosis are both exacerbated by the upregulation of miR-21 [20].

It became out that microRNA-21 had a distinct function, one that included regulating macrophage inflammation. The unique role that miR-21 may play in both healthy and diseased conditions makes it an attractive miRNA to research [19].

There is evidence that cardiac fibroblasts with downregulated PTEN levels via miR-21 exhibit elevated production of matrix metalloproteinase and abnormalities in the extracellular matrix [21].

Cardiac fibroblasts have also been shown to have SPRY1 down regulation, which results in reduced cell death. It is believed that PPARα targeting by miR-21, rather than SPRY1, is the main cause of fibrosis in the kidneys. There are probably many more direct and indirect miR-21 targets still to be found, as there have been many reported [20].

Psoriasis and miR-21

The fact that microRNA-21 is much more highly expressed in psoriasis skin lesions than in healthy skin suggests that it plays a role in the development of psoriasis [22].

Evidence that ultraviolet light treatment reduces miR-21 expression in psoriasis skin suggests a function for miR-21 in inflammatory skin conditions, however stays unaltered in skin that is in good condition even after prolonged sun exposure [23].

Psoriasis is now treatable with biological medicines that target important parts of the gene network that defines the disease. Results from experiments using viral vectors or liposome-encapsulated siRNAs to target critical genes in psoriasis have been encouraging [24].

As a possible therapeutic target for psoriasis, microRNA-21 may act as an upstream regulator of TIMP-3. The IL-6/Stat3 pathway may be activated as a result of increased miR-21, which may be a result of reduced transcriptional activity of Jun/activating protein 1 [AP-1].The therapy of psoriasis might be improved by targeting miR-21 [25].

Summary of Studies Investigating miR-21 Expression in Psoriasis Vulgaris (Table 1)

Across most studies, miR-21 was consistently found to be upregulated in lesional skin and blood-derived samples from psoriatic patients compared to healthy controls. Several studies showed a positive correlation between miR-21 levels and PASI scores, indicating its potential as a prognostic marker. Treatment with biologics (e.g., TNF-α inhibitors) often led to a decrease in miR-21 expression, suggesting its use as a therapeutic response biomarker. However, limitations such as small sample sizes, heterogeneous patient populations, and varied sample types were noted. Longitudinal studies are needed to validate these findings in larger cohorts.

Table 1: Summary of Studies Investigating miR-21 Expression in Psoriasis Vulgaris

Study (Author, Year)	Controls (n)	Psoriasis Patients (n)	Sample Type	Severity & Activity & Treatment	miR-21 Expression	Relation to Severity/Activity/Response	Limitations	Other Relevant Data
Sonkoly and colleagues, 2010 [31]	4 (microarray)26 (qRT-PCR)	3 (microarray)25 (qRT-PCR)	Skin biopsies (lesional)	Not quantified; no treatment	Upregulated: >1.7-fold by microarray; validated in qRT-PCR (**p<0.01**)	Not assessed	Small discovery set (n=3–4); cross-sectional; no clinical correlations	First global miRNA profiling in psoriasis skin
Gu and colleagues, 2011 [23]	No controls	12 PSO (pre-, mid-, post-NB-UVB)	Skin biopsies	Clinical response to NB-UVB: 9/11 "excellent/good"	Downregulated after NB-UVB (p = 0.003)	Decrease paralleled clinical improvement	No healthy control arm; small n; severity only by response category	Demonstrates therapy-induced modulation of miR-21
Alatas and colleagues, 2020 [9]	54	52 (PASI 7.9 ± 8.8)	Serum	Mostly topical (92.4%); 7.6% systemic	Downregulated: fold-change 0.237, p = 0.00039	No correlation with PASI or DLQI	Mild disease spectrum; mixed therapies; cross-sectional	Large panel (42 miRNAs) profiled in serum
Meisgen and colleagues, 2012 [10]	27	psoriasis non-lesional (n = 10) and psoriasis lesional skin (n = 25)	Skin (laser-microdissected)	T cell activation status; no PASI	Upregulated in both keratinocytes and activated T cells	Inhibition increased T cell apoptosis in vitro	Cell-based; functional assay only; no in vivo severity data	Links miR-21 to T cell survival in psoriasis
Sara S. Ashour and colleagues [32]	40	40 psoriasis vulgaris patients	Skin biopsies	PASI score: mean 11.96 ± 3.19 (range 7.3–20.3); treatment-naïve patients (no history of treatment or other dermatologic diseases); moderate severity group	miRNA-21 was markedly upregulated (Significantly increased in psoriasis patients (p < 0.001))	Significant negative correlation with K14 levels (r = -0.4, p = 0.012)	Cross-sectional design; relatively small sample size; limited to moderate plaque psoriasis; no longitudinal follow-up; no functional assays for miR-21 targets	-

Pathogenic and Immunological Roles of miR-21 in Psoriasis

Pathogenic Mechanisms

miR-21 plays a central role in the immunopathogenesis of psoriasis by orchestrating multiple molecular and cellular dysregulations. It notably suppresses apoptosis in activated T cells by downregulating tumor suppressors include programmed cell death 4 (PDCD4) and phosphatase and tensin homolog (PTEN), promoting the persistence of autoreactive T cells within psoriatic plaques [26,27].

Additionally, miR-21 contributes to keratinocyte hyperproliferation and stimulates the production of pro-inflammatory cytokines, amplifying the local immune response [28]. In macrophages, miR-21 skews polarization toward a pro-inflammatory (M1) phenotype, facilitating the secretion of matrix metalloproteinases (MMPs), which contribute to extracellular matrix degradation, tissue remodeling, and the chronicity of inflammation [29].

Another pivotal pathway regulated by miR-21 is the interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling axis. This pathway is highly upregulated in psoriatic lesions and is responsible for sustained epidermal inflammation and thickening [30].

Relevance to Disease Severity

Elevated miR-21 expression has been strongly associated with the severity of disease, reflecting both the inflammatory burden and keratinocyte dysfunction in psoriasis. Clinical data have consistently demonstrated a correlation between miR-21 levels and PASI scores, reinforcing its role as a prognostic indicator [25].

Furthermore, post-treatment reductions in miR-21 expression—notably following narrowband UVB phototherapy or biologic therapy targeting TNF-α—correlate with clinical improvement, highlighting its utility in monitoring disease activity and treatment response. These findings position miR-21 as a promising biomarker and a potential therapeutic target in the comprehensive management of psoriasis vulgaris [23].

3. Conclusion

miR-21 plays a role in the pathogenesis, progression, and therapeutic response of psoriasis vulgaris. Its upregulation in psoriatic lesions, association with disease severity, and modulation by various treatment modalities indicate that miR-21 may function as both a biomarker and a therapeutic target in clinical practice.

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