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MICRO-RNA-S AS MEDIATORS IN DEVELOPMENT OF PSORIASIS

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მიკრო-რნმ - შუამავალი ფსორიაზის განვითარებაში

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რეზიუმე

ფსორიაზი წარმოადგენს ქრონიკულ ანთებად დაავადებას, რომელსაც საფუძვლად უდევს ეპიგენეტიკურ-იმუნოლოგიური მექანიზმების რთული ურთიერთქმედება. მიუხედავად იმისა, რომ ფსორიაზის ზოგიერთი იმუნოლოგიური მექანიზმი შესწავლილია, დაავადების მთავარი გამომწვევი და წარმმართველი ფაქტორი ჯერ-ჯერობით კვლავ უცნობი რჩება. არაკოდირებადი რნმ-ების აღმოჩენამ და გენის ექსპრესიის რეგულაციაში მათი როლის აღწერამ გამოავლინა მათი მნიშვნელობა სხვადასხვა დაავადების პათოგენეზში, მათ შორის, ფსორიაზის დროსაც. მოცემულ ნაშრომში განვიხილავთ ფსორიაზის შემთხვევაში მიკრო-რნმ-თა შეცვლილი ექსპრესიის როლს. ასევე, მიმოვიხილავთ არსებულ ინფორმაციას ფსორიაზის დროს კონკრეტული მიკრო-რნმ-ების მომატებული ან დაქვეითებული (miR-21, miR-31, miR-99a, miR-125b, miR-155, miR-203) დონის გავლენის შესახებ დაავადების სხვადასხვა ეტაპსა და პროცესზე. კონკრეტულად კი, მათ მნიშვნელობას ანთებისა და კერატინოციტების პროლიფერაციის გაძლიერებასა და კერატინოციტების დარღვეულ დიფერენცირებაში, რაც არის ფუნდამენტური პათოგენეზური ფაქტორები ფსორიაზის დროს. აღწერილია მოცირკულირე მიკრო-რნმ-თა დონის კორელაცია დაავადების სიმძიმესთან, რაც აქტუალურს ხდის პოტენციურ ბიომარკერებად მათი გამოყენების შესაძლებლობას.

Introduction: Psoriasis is a common, chronic, immune-mediated inflammatory disease with a complex and not fully understood pathogenesis. According to the latest global data (2019), psoriasis affects approximately 0.53% of the world's population, equating to roughly 5.3 cases per 1,000 people, with the highest prevalence among individuals aged 40–64 [23]. Psoriasis presents in multiple subtypes, broadly categorized into non-pustular and pustular forms. Non-pustular psoriasis includes chronic plaque psoriasis (psoriasis vulgaris - the most common type of psoriasis), guttate psoriasis, inverse (flexural) psoriasis, erythrodermic psoriasis, nail psoriasis and psoriatic arthritis (PsA). Pustular psoriasis can be further divided into localized (acrodermatitis continua of hallopeau and palmoplantar pustulosis/Barber type) and generalized forms (von Zumbusch psoriasis) [20].

While non-pustular psoriasis typically presents as sharply demarcated erythematous plaques or papules with silvery-white scales (with variations depending on the subtype), pustular psoriasis is characterized by sterile pustules with distinct distribution patterns. Although both groups share some histopathological features, such as epidermal hyperplasia (acanthosis), parakeratosis, neutrophil accumulation (much more prominent in pustular forms), dilated blood vessels in the dermal papillae, and Munro's microabscesses (more common in plaque psoriasis), they can exhibit key differences [15]. After describing the immunological changes in psoriasis, it became clear that the immunological basis also differs between these two types of disease. While specific immunological mechanisms of pustular psoriasis have been characterized, the current research on the role of microRNAs (miRNAs) in psoriasis derives predominantly from studies on plaque psoriasis. This paper will, therefore, focus on examining microRNAs (miRNAs) in this subtype.

Immunopathogenesis of psoriasis: Current evidence indicates that psoriasis is a multifactorial disease arising from a combination of genetic predisposition (e.g., HLA-Cw6, HLA-Cw1, HLA-Cw12, and others), immune dysfunction, and environmental triggers (e.g., injuries, infections, stress, smoking, and certain medications). While the exact mechanisms linking these factors to immune dysfunction in psoriasis are still under investigation, it is established that they collectively drive immune cell recruitment and activation [17].

The characteristic histopathological changes observed in psoriasis are excessive proliferation, aberrant differentiation of epidermal keratinocytes, along with immune cell infiltration. Although the precise role of each immune cell requires further investigation, well-known immune cells involved in psoriasis include keratinocytes, dendritic cells, T-lymphocytes, neutrophils, and mast cells [25].

To understand the dynamic interplay of these immune cells, Sabat et al. divided the disease process into three phases: a sensitization phase, a silent phase, and an effector phase [19].

In response to some stimuli (infection/medication/trauma), keratinocytes become activated/stressed and release cytokines. Simultaneously, they secrete antimicrobial peptides (AMPs) - a group of small molecules involved in the innate immune response against pathogens, including bacteria, viruses, fungi, and parasites. Composed of 12-50 amino acids, AMPs possess broad-spectrum antimicrobial activity. LL37 binds to DNA/RNA nucleic acids, forming complexes among these. Along with LL37, ADAMTS-like protein-5 has also been identified as a psoriatic auto-antigen that is selectively expressed by injured epidermal melanocytes [4,17,25].

During the sensitization phase, in which no clinical symptoms are visible, formation of keratinocyte-derived antimicrobial peptide-nucleic acid complexes and pro-inflammatory cytokines trigger two activation pathways: (1) Type I interferons (IFN-α/γ) production through Toll-like receptors (TLR9 and TLR7) stimulation on plasmacytoid DCs (pDCs), and (2) TNF-α and IL-6 secretion via activation and maturation of myeloid DCs (mDCs) into fully functional dendritic cells through secretion of IFN-γ, TNF-α, IL-1ß, and IL-6 by keratinocytes, macrophages and other innate immune cells. Mature dendritic cells migrate to lymph nodes, presenting antigens to naïve T-cells. Through the expression of co-stimulatory molecules on their surface (e.g., CD80/CD86) and secretion of various cytokines (e.g., IL-12 for Th1; IL-6, TGF-β, IL-1β, and IL-23 for Th17; IL-6 and TNF-α for Th22), they drive the differentiation of T-cells into mature Th1, Th17, and Th22 subsets [4,19].

Regardless of the specific T-helper cell subtypes a naïve T cell differentiates into, its activation leads to the formation of distinct memory populations. While differentiation, otherwise named polarization of T-cells, determines the T cell's cytokine profile, the formation of memory T-cells determines the T cell's long-term behavior. In this sense, naïve T cells can produce an effector T cell, an effector memory T cell, or a central memory T cell. Effector T cells are short-lived, rapidly produces cytokines, and die after the immune response ends. Effector memory T cells circulate in the blood or peripheral tissue and quickly reactivate upon reexposure to antigen. Central memory T cells mainly recirculate between blood and lymph nodes, exhibit a long lifespan, and retain strong proliferative capacity [1,19].

During the silent phase, activated T cells migrate to the skin, some of them converting into tissue-resident memory T cells. These cells persist long-term and create chronic inflammatory milieu in both lesional and perilesional sites of psoriasis that is susceptible to activation [1,13,19].

During the effector phase, migrated T-cells release distinct cytokines. Activated Th1 cells produce IFN-γ, TNF-α, and IL-2; Th17 cells secrete IL-17A, IL-17F, IL-22, and TNF-α; Th22 cells predominantly release IL-22 and TNF-α. These cytokines act on keratinocytes, stimulating them, which leads to

proliferation, altered differentiation, and cellular stress, further promoting additional cytokine release. The IL-23/IL-17A axis was identified as a key driver factor in the development of psoriasis [4,19].

Consequently, elevated levels of pro-inflammatory cytokines (IL-6, IL-23, and IL-1β) disrupt Treg differentiation and stability, shifting the immune balance toward pathogenic Th17 responses, thereby exacerbating inflammation and autoimmunity. This Th17/Treg imbalance creates a chronic, self-reinforcing inflammatory loop and facilitates psoriatic plaque formation [25].

Epigenetic changes in psoriasis: After exploring the roles of genetics and environmental factors in the development of psoriasis, researchers are now investigating their interplay, particularly how environmental influences modify immune-related gene function through epigenetic mechanisms. Well-known epigenetic modifications include DNA methylation/demethylation, histone modifications, and changes regulated by non-coding RNAs, specifically microRNAs [16]. This paper will focus on the role of different microRNAs in the development of the disease.

MicroRNAs (miRNAs) are small non-coding RNAs, approximately 22 nucleotides long, that regulate gene expression post-transcriptionally. More than 2,500 microRNAs have been identified in humans from the microRNA database 2019. They function by targeting messenger RNAs (mRNAs), modulating their translation efficiency and/or stability via RNA-induced silencing complex and, therefore, regulating various biological processes, including developmental timing, cell death, cell proliferation, haematopoiesis, and nervous system patterning [8].

Current research has identified around 250 dysregulated miRNAs in psoriasis that contribute to disease pathogenesis by regulating cell growth, modulating keratinocyte proliferation, their differentiation, immune responses, cytokine production, as well as the activation of different T cells and regulation of Th1/Th2 balance [6,14]. Circulating miRNAs in psoriasis may also serve as potential biomarkers based on the fact that their different levels showed correlations with PASI (Psoriasis Area Severity Index) scores, therefore, disease severity [2,11].

A standardized classification system for miRNAs has not yet been established, primarily due to an incomplete understanding of their diverse functions. The current categorization of miRNAs in psoriasis often focuses on their functional roles, such as miRNAs regulating keratinocyte proliferation, their differentiation or inflammatory processes. However, this classification faces limitations because many miRNAs exhibit overlapping roles; a single miRNA may regulate both keratinocyte proliferation and inflammatory pathways (e.g., miR-31 enhances both processes in psoriasis).

Given this complexity, dysregulated miRNAs in psoriasis are often classified pragmatically by their expression levels, such as upregulated miR-21 or downregulated miR-125b-5p.

One of the most extensively studied miRNAs in psoriasis is miR-21, the expression level of which is increased in psoriatic plaques, dermal T-cells, and blood samples. It plays a significant role in cell proliferation, differentiation, apoptosis, and migration. By binding to CASP8 (caspase-8) mRNA, miR-21 inhibits cell apoptosis, promoting keratinocyte hyperproliferation [7].

Furthermore, miR-21 suppresses SMAD7 (the 7th member of the SMAD family), resulting in an elevated level of TGF-β1 (transforming growth factor-β1), which induces differentiation of naïve T-cells into Th17 cells and production of IL-17 [12]. TGF-β1 can further stimulate miR-21 transcription, creating a self-amplifying loop [5].

Elevated miR-21 also contributes to inflammation by downregulating epidermal TIMP-3 (tissue inhibitor of matrix metalloproteinase-3), thereby enhancing TNF-α secretion by keratinocytes and promoting inflammation. Interestingly, TNF-α by itself increases miR-21 transcription by triggering STAT3 (signal transducer and activator of transcription 3) [26].

Another well-studied microRNA is miR-31, which is overexpressed in psoriatic lesions. It targets PPP6C (protein phosphatase 6) and FIH-1 (factor-inhibiting hypoxia-inducible factor 1). PPP6C is a negative cell cycle regulator, and by inhibiting this gene, miR-31 contributes to keratinocyte proliferation and epidermal hyperplasia. Along with that, high levels of miR-31 repress STK40 (serine/threonine kinase 40), a negative regulator of the NF-kB (nuclear factor-kB) signaling pathway, therefore activating keratinocyte hyperproliferation and release of pro-inflammatory cytokines, such as TNF-α, IL-1ß, IL-6, IL-8, IL-17, IL-23. The inflammatory cytokines themselves activate NF-kB signaling and induce miR-31. These cytokines also affect keratinocytes, leading to their activation [26,28].

The functional role of miR-31 appears complex, with evidence supporting its involvement in keratinocyte proliferation and differentiation. However, its effects appear context-dependent. On the one hand, miR-31 may promote keratinocyte differentiation by downregulating FIH-1, stabilizing HIF-1α (hypoxia-inducible factor), and modulating the Notch signaling pathway. On the other hand, miR-31 overexpression exacerbates psoriasis by activating the STAT3/p53 axis, thereby suppressing apoptosis and promoting disease progression [18,26].

Another miRNA involved in psoriasis pathogenesis is miR-155. MiR-155 level is significantly increased in psoriasis skin lesions and peripheral blood mononuclear cells (PBMCs). Increased expression of miR-155 in PBMCs appears to correlate with PASI and disease severity [3]. Overexpression of miR-155 inhibits PTEN (phosphatase and tension homolog), accumulating PIP3 (phosphatidylinositol-3,4,5-trisphosphate), which subsequently enhances AKT (protein kinase B) activity, resulting in suppressed apoptosis and increased keratinocyte proliferation [26]. MiR-155 was shown to potentially play a role in psoriasis development by increasing the inflammatory response via the NF-kB pathway [10]. MiR-155 targets CTLA4 (cytotoxic T lymphocyte-associated antigen 4), disrupting its immune-inhibitory function and promoting T-cell hyperactivation. This contributes to an inflammatory milieu favouring Th17 differentiation. Additionally, miR-155 drives Th17 cell polarization through direct suppression of SOCS1 (suppressor of cytokine signaling 1), a negative regulator of the JAK-STAT signaling pathway. By inhibiting SOCS1, miR-155 enhances STAT3 activation, further amplifying IL-17 production and exacerbating psoriatic inflammation [29].

Another keratinocyte-derived microRNA, miR-203, is significantly upregulated in psoriasis. Through inhibition of SOCS3, miR-203 activates STAT3 signaling - a key pathway regulating keratinocyte proliferation, differentiation, and inflammatory responses. Activation of STAT3 triggers overexpression of IL-6, TNF-ß, and EGFR (epidermal growth factor receptor), ultimately leading to apoptosis suppression, uncontrolled keratinocyte accumulation, and sustained inflammation [14].

Notably, miR-203 expression is further amplified by pro-inflammatory cytokines (IL-1α, IL-17A, IL-6, TNF-α), creating a loop that exacerbates psoriatic pathology. An additional mechanism of miR-203 is directly targeting tumor protein 63 (p63), a p53 family member essential for stem-cell maintenance. Repression of p63 by miR-203 contributes to aberrant keratinocyte proliferation [30].

Several other upregulated miRNAs in psoriasis show promising results as biomarkers for disease severity. Løvendorf et al. revealed that miR-223 and miR-143 could serve as potential systemic biomarkers in psoriasis because of their higher expression levels in PBMCs of psoriasis patients compared to healthy controls. Additionally, both miRNAs positively correlation with PASI scores, indicating their potential as disease severity markers [11]. Feng et al. studied miR-126 and concluded that upregulated miR-126 in lesional skin tissue promotes hyperproliferation of keratinocytes and inflammation in psoriasis correlating with increased disease risk and severity [2]. MiR-1266 could also be a potential biomarker, as its high serum levels were inversely correlated with psoriasis severity index (PASI) and BSA [21]. One study

discovered elevated levels of miR-19a in the hair roots of psoriatic patients and concluded that this microRNA could serve as a disease marker [6].

Several microRNAs that are downregulated in psoriasis have been described. One of the most downregulated microRNAs is miR-125b. It is expressed by resident cells (fibroblasts, keratinocytes, and melanocytes) and targets multiple genes involved in keratinocyte hyperproliferation and inflammation. MiR-125b suppresses FGFR2 (fibroblast growth factor receptor 2). Its downregulation in psoriasis leads to FGFR2 overexpression, driving keratinocyte proliferation [27]. Ferrarese et al. showed that miR-125b targets USP2 (ubiquitin-specific peptidase 2), a negative regulator of keratinocyte proliferation. Reduced miR-125b levels increase USP2, further promoting proliferation [24]. Zheng et al. identified AKT3 (an AKT isoform) as another miR-125b target. The inverse correlation between miR-125b and AKT3 in psoriasis activates the signaling pathway, enhancing keratinocyte proliferation [31].

MiR-99a is also downregulated in psoriasis. In healthy skin, miR-99a regulates the expression of IGF1R (insulin-like growth factor 1 receptor), inhibits keratinocyte proliferation, and promotes its differentiation. In psoriasis, loss of miR-99a leads to IGF1R overexpression, contributing to uncontrolled proliferation and epidermal hyperplasia [9]. Downregulation of miR-99a in psoriasis also results in FZD5/FZD8 overexpression, activating downstream factors β-catenin and cyclinD1, further accelerating keratinocyte proliferation [22].

Conclusion: Understanding the pathogenetic mechanisms of psoriasis is essential for developing targeted therapies that address the root causes of the disease rather than merely alleviating symptoms. Currently, there is lack of unified, objective biomarkers for monitoring, or predicting the recurrence of psoriasis. While the exact pathogenesis of psoriasis remains incompletely understood, emerging evidence suggests that epigenetic and immunological pathways do not operate in isolation but instead interact synergistically, forming a complex self-amplifying inflammatory network that drives disease progression.

MiRNAs have emerged as a key part of psoriasis, in which specific miRNAs have been shown to drive inflammation, promote keratinocyte hyperproliferation and abnormal differentiation. However, the precise mechanism of these miRNAs remains unclear, and no pathognomic miRNAs for psoriasis has yet been identified.

The complexity of disease is determined by several factors. First, different signaling cascades cooperate to alter keratinocyte behavior, sustain inflammation, and dysregulate immune responses. Second, a single miRNA can be regulated by multiple pathways, and one miRNA may influence several disease-relevant processes. Moreover, a single miRNA may exhibit divergent and even opposite functions within the same disease process. This network makes it challenging to identify a primary etiological trigger in psoriasis and highlights the importance of further investigation of the miRNAs spectrum.

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SUMMARY

Psoriasis is a chronic inflammatory skin disease driven by complex epigenetic-immunological interactions. Although some immunological mechanisms have been characterized, the primary initiating factor of psoriasis remains elusive. The discovery of non-coding RNAs and their role as gene expression regulators has revealed their critical involvement in the pathogenesis of different diseases, including psoriasis.

This paper examines the contribution of specific dysregulated miRNAs to psoriatic inflammation, focusing on the most upregulated or downregulated (miR-21, miR-31, miR-99a, miR-125b, miR-155, miR-203) species. We discuss how these miRNAs form pathogenic feed-forward loops, that amplify inflammation and sustain keratinocyte dysfunction, which are fundamental factors in psoriasis, The intricate crosstalk between these miRNAs and Th17-associated cytokines (IL-17, IL-23) further complicates the disease network. Finally, we highlight miRNAs as potential biomarkers and therapeutic targets in psoriasis management.

Keywords: psoriasis, epigenetic, miRNAs, immunopathogenesis, biomarkers