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MicroRNA Signatures in Psoriatic Arthritis: From Pathogenesis to Precision Medicine

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ABSTRACT

Psoriatic arthritis (PsA) is a chronic inflammatory disorder caused by complex interactions among genetic, environmental, and epigenetic factors. MicroRNAs (miRNAs) have emerged as pivotal regulators of PsA pathogenesis by orchestrating synovial inflammation, osteoclastogenesis, immune dysregulation, and tissue remodeling. This review synthesizes the current evidence on dysregulated miRNA signatures in PsA, highlighting their dual roles as pathogenic mediators and diagnostic/therapeutic tools. Key upregulated miRNAs (e.g., miR-146a-5p, miR-21-5p, miR-221-3p, miR-941, and miR-130a-3p) amplify inflammation via NF-κB, IL-17/IL-23, and TNF-α pathways, while downregulated miRNAs (e.g., let-7b-5p, miR-30e-5p, miR-125b, and miR-125a-3p) disrupt protective checkpoints. Clinically, multi-miRNA serum panels (e.g., miR-221-3p/miR-130a-3p/miR-146a-5p/miR-151-5p/miR-26a-5p/miR-21-5p) achieve a high diagnostic accuracy (AUC >0.90), outperforming single biomarkers. Extracellular vesicle (EV)-encapsulated miRNAs enhance disease specificity and correlate with joint involvement. Therapeutically, miRNA levels predict treatment response (e.g., high miR-221-3p/miR-130a-3p levels associated with improved EULAR responses), and novel delivery systems (e.g., FNA-miR-125b) show efficacy in preclinical models. These findings suggest that miRNA signatures can be used as integrated tools for precision diagnosis, prognosis, and targeted therapy in PsA.

Keywords: **MicroRNA, Psoriatic Arthritis, Pathogenesis, Extracellular Vesicles, Expression Signatures.**

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INTRODUCTION

Psoriatic arthritis (PsA) is a complex chronic inflammatory disease that affects approximately 30% of psoriasis patients (PsO) and is characterized by an intricate interplay between genetic predisposition, environmental triggers, and epigenetic regulatory mechanisms. Among the most significant epigenetic modulators emerging in PsA research are microRNAs (miRNAs), small non-coding RNA molecules measuring approximately 18-25 nucleotides that function as post-transcriptional regulators of gene expression. These molecular switches have revolutionized our understanding of PsA pathogenesis, offering unprecedented insights into disease mechanisms while simultaneously presenting promising avenues for precise diagnosis, prognosis, and therapeutic intervention[1].

The foundational significance of miRNAs in PsA stems from their dual roles as both pathogenic drivers and regulatory guardians within the inflammatory cascade. Unlike traditional biomarkers that merely reflect disease states, miRNAs actively participate in orchestrating the molecular networks that govern synovial inflammation, keratinocyte

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hyperproliferation, immune cell activation, and bone remodeling processes that are characteristic of psoriatic disease. This functional involvement positions them as particularly valuable therapeutic targets, as modulating miRNA expression can potentially address the underlying disease mechanisms rather than merely suppressing downstream inflammatory mediators[2].

Recent research has identified distinctive miRNA expression patterns that differentiate PsA from both healthy individuals and patients with cutaneous-only psoriasis[3]. These signatures encompass both dramatically upregulated inflammatory miRNAs, such as miR-146a-5p, miR-21-5p, miR-221-3p, and miR-130a-3p, which drive pathological processes including osteoclastogenesis, IL-17/IL-23 axis activation, and TNF-α signaling amplification[4]. Conversely, the coordinated downregulation of protective miRNAs such as let-7b-5p, miR-30e-5p, and miR-125b removes critical regulatory checkpoints that normally suppress excessive inflammation and maintain tissue homeostasis[2,3].

The diagnostic potential of miRNA signatures has demonstrated remarkable clinical promise, with individual miRNAs achieving area under the curve (AUC) values exceeding 0.86-0.94 for PsA detection compared to healthy controls. More sophisticated approaches utilizing multi-miRNA panels, particularly the validated six-miRNA serum signature (miR-221-3p, miR-130a-3p, miR-146a-5p, miR-151-5p, miR-26a-5p, and miR-21-5p), have achieved even higher diagnostic accuracy, with AUC values approaching 0.90[1]. These performance metrics position miRNA-based diagnostics as potentially superior alternatives to current clinical markers, addressing the critical clinical need for reliable early detection tools in a disease where diagnostic delays as short as six months can result in irreversible joint damage[5].

Extracellular vesicle (EV)-encapsulated miRNAs represent a particularly innovative dimension of PsA biomarker research[6]. These membrane-bound vesicles actively transport miRNAs between cells, serving both as intercellular communication mediators and remarkably stable biomarker platforms in circulation. Studies have demonstrated that EV-derived miRNAs such as let-7b-5p and miR-30e-5p exhibit superior disease specificity compared to total serum miRNAs, with their reduced levels directly correlating with joint involvement and disease activity measures. The selective packaging of miRNAs into EVs suggests active regulatory processes that may reflect tissue-specific disease mechanisms, making them particularly valuable for distinguishing PsA from cutaneous-only psoriasis[3,7].

The therapeutic dimensionality of miRNA research in PsA extends beyond biomarker applications, to encompass direct therapeutic modulation. Treatment response prediction represents an immediately translatable clinical application, with baseline miRNA levels demonstrating significant associations with therapeutic outcomes, according to the EULAR response criteria[8]. Paradoxically, patients with higher baseline expression of specific inflammatory miRNAs show better treatment responses, likely reflecting the presence of active, treatment-responsive inflammatory processes rather than chronic, fibrotic disease states. Advanced delivery technologies, particularly framework nucleic acid (FNA) systems, have demonstrated the feasibility of topical miRNA replacement therapies [9].

Preclinical studies using FNA-miR-125b have shown superior efficacy compared with conventional treatments, such as betamethasone, in addressing both cutaneous and inflammatory manifestations[10]. These technological advances suggest that comprehensive miRNA-based therapeutics could potentially restore all dysregulated regulatory networks simultaneously, offering more durable and mechanistically

comprehensive treatment approaches than current cytokine-targeted therapies [11]. The mechanistic integration of miRNA dysregulation in PsA reveals sophisticated regulatory networks where individual miRNAs function as nodes within interconnected pathways governing osteoimmunology, cytokine signaling, and tissue remodeling[12].

This system-level involvement means that miRNA signatures provide molecular readouts of disease activity across multiple pathogenic axes simultaneously, explaining their superior diagnostic performance and therapeutic predictive value compared to single-pathway biomarkers[13,14]. Over the past decade, circulating and tissue-derived miRNA profiles have emerged as sensitive readouts of both cutaneous and musculoskeletal disease activities, offering novel biomarkers and drug targets. This review synthesizes the current knowledge on the most robust PsA-related miRNAs, contextualizes them within mechanistic pathways, and appraises their clinical utility.

Molecular Landscape of miRNA Dysregulation in PsA

Up-regulated miRNAs Driving Inflammation in Psoriatic Arthritis

The inflammatory landscape of PsA is orchestrated by a sophisticated network of dysregulated miRNAs that act as molecular switches that modulate critical pathogenic pathways. Biomarkers and potential treatment targets, these elevated miRNAs provide light on the intricate relationship between epigenetic regulation and chronic inflammation in this debilitating inflammatory joint disease.

miR-146a-5p

miR-146a-5p is the most extensively characterized inflammatory miRNA in psoriatic arthritis, exhibiting profound upregulation in CD14 + monocytes from patients with PsA compared to both psoriasis-only patients and healthy controls. This miRNA functions as a central orchestrator of bone destruction through multiple interconnected mechanisms[5]. Functionally, miR-146a-5p promotes osteoclastogenesis by targeting and repressing IRAK1, thereby potentiating the NF-κB signaling cascades that drive inflammatory bone resorption. The clinical significance of this dysregulation becomes evident when examining its correlation with disease activity markers elevated miR-146a-5p expression directly correlate with C-RP levels and are associated with enhanced osteoclast formation and functional bone resorption capacity[15].

The therapeutic implications of miR-146a-5p are particularly interesting. Following successful biologic therapy, aberrantly elevated miR-146a-5p expression in PsA patients becomes comparable to that in healthy controls, suggesting its potential utility as a treatment response biomarker[2]. This normalization parallels clinical improvement and reduction in inflammatory markers, positioning miR-146a-5p as both a mechanistic driver and measurable indicator of therapeutic efficacy. The involvement of microRNAs extends beyond simple inflammation, as they participate in the late-phase inflammatory feedback loop through negative regulation of NF-κB signaling, representing a compensatory mechanism that attempts to limit excessive inflammatory responses[15].

miR-21-5p

miR-21-5p is a pivotal regulator of the IL-17/IL-23 inflammatory axis, demonstrating significant upregulation in both early PsA and psoriasis cutaneous disease compared to that in HCs. This miRNA exhibits particularly pronounced elevation in patients with early PsA compared to psoriasis-only patients, establishing it as a potential biomarker for joint involvement progression[16]. The mechanistic basis for miR-21-5p inflammatory role lies in its direct modulation of the IL-17/IL-23 cytokine

network; when miR-21-5p levels are elevated, IL-17 and IL-23 are concurrently upregulated, while the anti-inflammatory cytokine TGF-β1 is downregulated [17].

The therapeutic relevance of miR-21-5p is apparent through its dynamic response to methotrexate treatment. After 24 weeks of MTX therapy, miR-21-5p expression was significantly downregulated in PsA patients, with this reduction correlating directly with actively inflamed joint counts and disease activity scores[18]. Importantly, the correlation extends to related inflammatory mediators, including CXCL10 and IL-23, suggesting that miR-21-5p functions as a central node in the inflammatory network rather than as an isolated regulatory element. The ability of microRNA to suppress T-cell apoptosis while augmenting the IL-17/IL-23 axis positions it as a critical contributor to chronic synovial inflammation[19].

miR-221-3p

miR-221-3p is a key amplifier of TNF-α-mediated inflammation, showing significant upregulation in both PsA and PsO, with particularly strong correlations with disease severity markers.[20] This microRNA demonstrates exceptional diagnostic performance, with ROC curve analysis revealing AUC values exceeding 0.86 for PsA detection, positioning it as one of the most robust single biomarkers for disease identification. The mechanistic basis for miR-221-3p's inflammatory role involves the regulation of TNF-α degradation pathways by microRNA targets and down-regulates TIMP3 of Tissue Inhibitor of Metalloproteinase-3), a protein crucial for TNF-α degradation, leading to pathological TNF-α accumulation[21].

Clinical studies have demonstrated that miR-221-3p levels correlate positively with disease duration and Psoriasis Area and PASI scores, indicating its involvement in disease progression. Furthermore, patients with higher baseline levels of miR-221-3p are significantly more likely to achieve good therapeutic responses according to EULAR criteria, suggesting that paradoxically, higher inflammatory miRNA levels may predict better treatment outcomes[22]. This phenomenon likely reflects the presence of more active treatment-responsive inflammatory processes rather than chronic fibrotic disease states. The dual role of miRNAs in promoting keratinocyte proliferation and inflammatory cytokine production makes them central mediators of both cutaneous and articular disease manifestations[1].

miR-941

miR-941 represents a newly identified, highly specific mediator of osteoclast-driven joint destruction in psoriatic arthritis, showing selective upregulation in CD14 + monocytes from PsA patients, but not in psoriasis-only patients or HCs. This miRNA functions through a unique WNT16 suppression mechanism by targeting and repressing WNT16 expression, miR-941 removes critical osteoclast inhibitory signals, leading to enhanced osteoclast differentiation and pathological bone resorption[23]. Results from functional experiments show that there is a clear causal link between miR-941 and joint destruction. Specifically, miR-941 suppression by RNA interference fully abolishes increased osteoclast production and bone resorption activity in cells obtained from PsA patients[24].

The clinical significance of miR-941 is underscored by its disease-specific expression patterns and responsiveness to treatment. Unlike other inflammatory miRNAs that may be elevated across multiple inflammatory conditions, miR-941 shows remarkable specificity for PsA versus psoriasis cutaneous disease alone[25]. Following successful treatment, elevated miR-941 expression in PsA patients becomes revoked, paralleling clinical improvement and suggesting its utility as both a diagnostic marker and a treatment response indicator. One possible treatment target for preventing or reversing joint degeneration in

PsA26 might be microRNAs because of their role in the WNT signaling system, which links it to core bone homeostasis processes [26].

miR-130a-3p

miR-130a-3p functions as a crucial component of multi-miRNA diagnostic signatures for psoriatic arthritis, consistently appearing in validated biomarker panels in multiple independent studies[2]. This miRNA demonstrates significant upregulation in PsA patients compared to healthy controls and shows a strong correlation with disease activity measures, including DAPSA scores. As part of the six-miRNA serum signature (including miR-221-3p, miR-130a-3p, miR-146a-5p, miR-151-5p, miR-26a-5p, and miR-21-5p), miR-130a-3p contributes to diagnostic panels achieving AUC values exceeding 0.90 for PsA identification[1].

The therapeutic implications of miR-130a-3p extend from diagnosis to treatment prediction and monitoring. Patients with higher baseline levels of miR-130a-3p demonstrated significantly better therapeutic responses according to the EULAR criteria, suggesting that this miRNA may serve as a pretreatment stratification marker to identify patients most likely to benefit from specific therapeutic interventions[27]. In PsA care, miRNA is a dependable component of precision medicine methods due to its constant presence across many independent validation cohorts and high connection with recognized disease activity measures28[28].

These upregulated miRNAs collectively represent a sophisticated regulatory network that drives and sustains the chronic inflammatory processes characteristic of psoriatic arthritis. Their therapeutic modulation through targeted interventions offers promising avenues for precision medicine approaches, potentially allowing for more effective, personalized treatment strategies that address the underlying epigenetic drivers of this complex inflammatory disease[1–3,15].

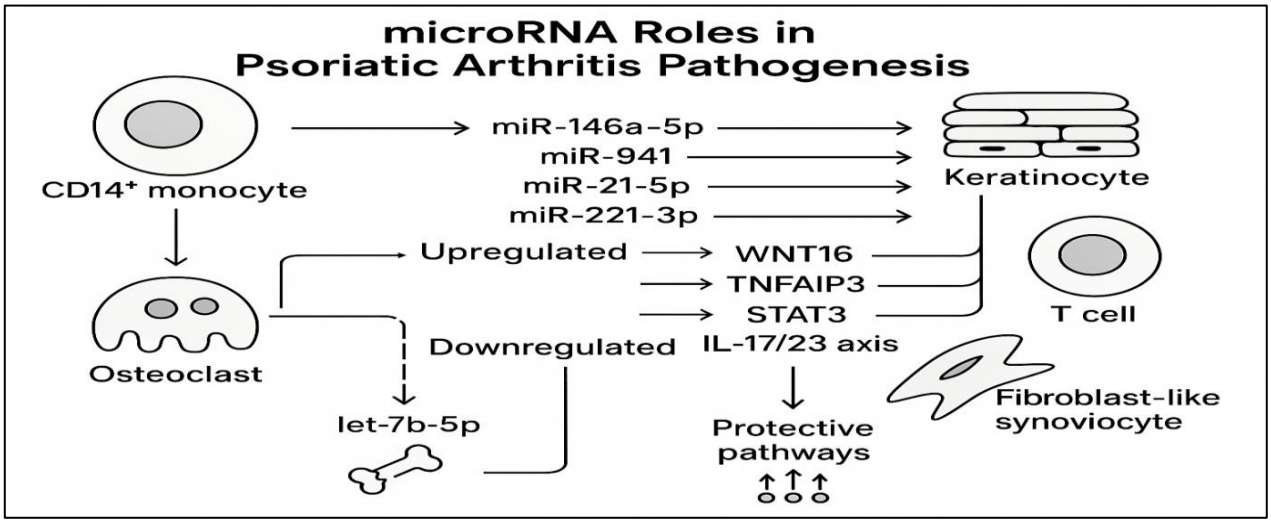

Figure: Illustrative network of microRNA-mediated pathways driving inflammation and bone erosion in psoriatic arthritis.

Down-regulated miRNAs with Protective Roles

The landscape of PsA pathogenesis is not solely driven by inflammatory miRNAs; the coordinated suppression of protective microRNAs that normally function as molecular guardians against excessive inflammation, keratinocyte hyperproliferation, and joint destruction is equally important. These downregulated miRNAs represent lost

checkpoints in the regulatory network, and their therapeutic restoration offers promising avenues for disease intervention and precision medicine.

let-7b-5p

let-7b-5p emerges as one of the most clinically relevant protective miRNAs in psoriatic arthritis, showing much lower amounts in extracellular vesicles produced from plasma in individuals with PsA when compared with PsO in patients with cutaneous-only disease. This miRNA functions as a central regulator of the inflammatory cytokine network, with multiple validated targets that collectively suppress pathogenic inflammatory cascades[29]. The clinical significance of let-7b-5p becomes evident through its diagnostic performance ROC analysis reveals an AUC of 0.68 for distinguishing PsA from psoriasis cutaneous disease. Importantly, let-7b-5p levels showed a positive correlation with miR-30e-5p expression, with the strongest correlation observed in PsA patients, suggesting coordinated regulatory mechanisms between these protective miRNAs[30].

The protective effect of let-7b-5p in PsA stems from its direct suppression of key pathogenic molecules. It targets IL-6, a pro-inflammatory cytokine markedly elevated in PsA compared to cutaneous psoriasis, which critically drives synovial and systemic inflammation[31]. Furthermore, let-7b-5p inhibits HMGA1 and HMGA2, proteins implicated in joint inflammation and pathological tissue remodeling characteristic of inflammatory arthritis[7]. Crucially, let-7b-5p directly targets PRDM1 (encoding Blimp-1), a transcription factor essential for TNF-α-induced osteoclast formation and inflammatory bone destruction. Consequently, the observed decrease in let-7b-5p levels in PsA patients alleviates this regulatory suppression, facilitating excessive osteoclast activity and bone resorption[30].

The therapeutic implications of let-7b-5p extend beyond its anti-inflammatory effects. The role of microRNAs is context-dependent, and they can function as TLR7 ligands and promote inflammation in certain settings, demonstrating protective effects against inflammation-associated pathological processes in PsA[2]. This dual functionality highlights the complex regulatory networks governing inflammatory responses, and suggests that let-7b-5p replacement therapy should be carefully calibrated to restore protective functions without triggering paradoxical inflammatory responses. Reduced quantities of let-7b-5p in extracellular vesicles in circulation could be an indication of alterations taking place in the tissues of the joints, potentially contributing directly to PsA pathogenesis through the loss of local anti-inflammatory control mechanisms[7].

miR-30e-5p

Plasma extracellular vesicles from patients with PsA reveal considerably lower levels of miR-30e-5p, a crucial protector of the NF-κB signaling pathway, in comparison to those from patients with psoriasis cutaneous illness. This microRNA demonstrates diagnostic utility for PsA detection, with an AUC of 0.69 for PsA detection, and importantly shows a trend toward negative correlation with disease severity measures including DAS28, BASDAI, and the number of swollen joints[29]. This inverse relationship between miR-30e-5p levels and disease activity suggests that the progressive loss of this protective miRNA correlates with worsening joint inflammation and structural damage[32].

The protective mechanism of miR-30e-5p involves direct suppression of BMI1, a known activator of the NF-κB pathway. Since BMI1 deficiency inhibits NF-κB-driven arthritis in mice[33]. miR-30e-5p acts as an upstream negative regulator, thereby mitigating the NF-κB-mediated inflammation responsible for PsA's cutaneous and articular manifestations[29]. Additionally, miR-30e-5p downregulates LRP6, a key Wnt pathway co-receptor implicated in bone metabolism and inflammatory joint

processes. Pathological bone alterations in PsA, such as syndesmophyte formation and bone erosion [3], are linked to dysregulated Wnt signaling, in which LRP6 participates. Evidence for miR-30e-5p's wider significance in inflammatory arthritis comes from findings of its reduced abundance in extracellular vesicles derived from RA patient PBMCs relative to healthy individuals[7].

This cross-disease relevance suggests that miR-30e-5p functions as a fundamental checkpoint against inflammatory joint destruction in multiple arthritides. The coordinated reduction of miR-30e-5p and let-7b-5p in PsA patients indicates that these protective miRNAs may function within integrated regulatory networks, and their simultaneous loss creates permissive conditions for sustained inflammation and joint damage[34]. The therapeutic restoration of miR-30e-5p levels represents an attractive intervention strategy, particularly given its dual role in suppressing both inflammatory signaling (through BMI1/NF-κB) and pathological bone remodeling (through LRP6/Wnt pathway modulation). The strong correlation between miR-30e-5p levels and joint-specific disease activity measures suggests that this miRNA could serve both as a biomarker for monitoring treatment response and as a direct therapeutic target for preventing or reversing joint damage in PsA[32].

miR-125b

miR-125b is the most extensively characterized protective miRNA in psoriatic disease, representing one of the most dramatically downregulated miRNAs in psoriatic skin and demonstrating profound regulatory control over keratinocyte proliferation, differentiation, and inflammatory responses[35]. This miRNA functions as a master regulator of epidermal homeostasis by targeting multiple growth factor receptors and signaling pathways that drive pathological keratinocyte behavior. The clinical relevance of miR-125b is underscored by its consistent downregulation across multiple psoriatic disease studies and its validation as a therapeutic target in preclinical models[36].

The primary mechanism by which miR-125b exerts its protective effects involves direct targeting of FGFR2, a receptor that is upregulated in psoriatic keratinocytes and drives their hyperproliferative phenotype[37]. The miR-125b decreases FGFR2 expression and, by extension, the proliferation of primary human keratinocytes by base-pairing with the 3'-UTR of FGFR2 mRNA. Overexpression of miR-125b in primary human keratinocytes inhibits proliferation and increases the expression of many recognized markers of differentiation, indicating a substantial regulatory link. In contrast, normal differentiation processes are postponed and cell proliferation is enhanced when endogenous miR-125b is inhibited [38].

Beyond FGFR2, miR-125b targets multiple pathways critical to psoriatic pathogenesis. The miRNA directly targets AKT3, and overexpression of miR-125b blocks the AKT pathway while inhibiting the proliferation of human epidermal keratinocytes[36]. AKT3 is a key component of the PI3K/AKT survival and proliferation pathway, and its dysregulation contributes to the hyperproliferative keratinocyte phenotype that is characteristic of psoriasis. Additionally, miR-125b inhibits the Notch signaling system by targeting BRD4, which stands for Bromodomain-containing protein 4. To further modulate keratinocyte proliferation, miR-125b inhibits BRD4, which in turn decreases the production of Jagged-1, an essential ligand in the Notch pathway [38].

The therapeutic potential of miR-125b has been demonstrated through innovative delivery approaches using Framework Nucleic Acids (FNA). In preclinical studies, topical application of FNA-miR-125b cream demonstrated superior efficacy compared to betamethasone treatment in mice with imiquimod-induced psoriasis [36].

The levels of inflammatory cytokines, PASI scores, and epidermal thickness were all significantly reduced after therapy with FNA-miR-125b. Most importantly, the treatment significantly decreased the expression of validated target mRNAs, including TNF-α and STAT3, compared with untreated controls. The FNA delivery system overcomes the traditional limitations of miRNA therapy, including poor stability and limited tissue penetration, making topical miR-125b replacement a viable therapeutic approach[38]. miR-125b also targets USP2, the ablation of which in keratinocytes lowers proliferation rates and enhances differentiation. This targeting relationship further reinforces miR-125b's role as a comprehensive regulator of keratinocyte biology, influencing not only proliferation and differentiation, but also protein stability and cellular stress responses. The coordinated targeting of multiple pathways FGFR2/growth factor signaling, AKT3/survival pathways, BRD4/Notch signaling, and USP2/protein stability–positions miR-125b as a central hub in the regulatory network governing epidermal homeostasis[37].

miR-125a-3p

miR-125a-3p is a specialized protective miRNA that specifically targets the TLR4/NF-κB inflammatory axis, demonstrating significant downregulation in PsO, psoriatic inflammatory cell models, and imiquimod-induced psoriatic mouse models. This miRNA functions as a direct upstream inhibitor of innate immune activation, that target TLR4, an important pattern recognition receptor that triggers inflammatory cascades in response to molecular patterns associated with both pathogens and injury [39]. The clinical significance of miR-125a-3p is evidenced by its inverse correlation with disease severity in patients with lower miR-125a-3p expression, demonstrating higher PASI scores, and more severe inflammatory manifestations[40].

The mechanistic basis for miR-125a-3p protective function lies in its direct targeting of TLR4, confirmed through luciferase reporter assays demonstrating that miR-125a-3p mimics significantly suppress TLR4 3' UTR luciferase activity[39]. TLR4 expression is significantly elevated in psoriatic skin tissues and correlates positively with PASI scores, whereas miR-125a-3p expression is negatively correlated with TLR4 protein levels. This inverse relationship establishes a clear regulatory hierarchy, where loss of miR-125a-3p permits aberrant TLR4 up-regulation, leading to sustained inflammatory activation. Functionally, miR-125a-3p overexpression suppresses keratinocyte proliferation, blocks the NF-κB and IL-1β pathways, and reduces the expression of inflammatory genes associated with psoriasis [41].

The therapeutic potential of miR-1.25a-3p has been validated in preclinical studies, demonstrating that intradermal injection of agomiR-125a-3p in imiquimod-induced psoriatic mouse models significantly reduced psoriasis-like inflammation[40]. This treatment effectively suppressed epidermal hyperplasia, reduced inflammatory infiltration, and normalized the expression of inflammatory mediators. The mechanism by which miR-125a-3p protects keratinocyte proliferation and inflammation gene expression is that it regulates the TLR4/NF-κB signaling axis. When TLR4 expression is artificially raised, the positive effects of miR-125a-3p mimics on these processes are reversed [42].

The TLR4/NF-κB, targeted by miR-125a-3p, represents a fundamental mechanism of innate immune activation that is particularly relevant to psoriatic disease pathogenesis[39]. Molecular patterns associated with pathogens or damage to tissues caused by inflammation or stress may activate TLR4. Sustained activation of this pathway creates a feed-forward loop, where inflammatory tissue damage generates additional TLR4 ligands, perpetuating chronic inflammation. By targeting TLR4 directly, miR-

125a-3p functions as a circuit breaker that prevents the pathological amplification of inflammatory responses[40].

CONCLUSIONS

Dysregulated miRNAs are central to PsA pathogenesis. Pro-inflammatory miRNAs (e.g., miR-146a-5p, miR-21-5p, miR-221-3p, and miR-941) drive osteoclast activation, cytokine amplification (TNF-α, IL-17/IL-23), and bone erosion, while loss of protective miRNAs (e.g., let-7b-5p, miR-30e-5p, and miR-125b) removes critical breaks in inflammation and tissue damage. Multi-miRNA serum panels achieve superior diagnostic accuracy in distinguishing PsA from cutaneous psoriasis and healthy controls. EV-encapsulated miRNAs (e.g., reduced let-7b-5p/miR-30e-5p) offer enhanced specificity for joint involvement. aseline miRNA levels (e.g., high miR-221-3p/miR-130a-3p) predict the treatment response to biologics and methotrexate. miRNA restoration (e.g., FNA-delivered miR-125b) or inhibition (e.g., anti–miR-941) shows promise in preclinical models, surpassing conventional therapies for suppressing inflammation and joint destruction. miRNA signatures provide a system-level view of disease activity, enabling early diagnosis (critical to prevent irreversible joint damage) and personalized treatment strategies that target upstream epigenetic drivers rather than downstream cytokines alone.

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