

The Importance of MicroRNAs in Normal and Psoriatic Skin

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ABSTRACT

Psoriasis is a systemic inflammatory skin condition characterised by raised and scaly skin lesions resulting from different factors, including the immune system as well as environment. The exact mechanism of psoriasis pathogenesis is not yet completely deciphered. MicroRNAs (**miRNAs**) are a class of small, non-coding RNAs that represent one of the most abundant classes of gene-regulators. Implication of miRNAs in psoriasis was first reported by Sonkoly et al. where different miRNA expression profiles were observed in psoriasis-affected skin compared with healthy human skin and atopic dermatitis affected skin. More than 250 miRNAs, found in peripheral blood or in involved psoriatic skin, have already been reported as aberrantly expressed in psoriasis tissue. As evidence for the role of miRNAs in the psoriasis pathogenesis and other inflammatory skin diseases is rapidly accumulating and novel associations for miRNAs in psoriasis are identified, the relevance of miRNAs as biomarkers in skin disease increases. Understanding of miRNA mediated gene regulation has enormous potential to grant an insight into the mechanisms and key players involved in the pathogenesis of psoriasis and to contribute to the development of future microRNA based therapies. In this article, we review the current literature, gathering information about the role of microRNAs in the pathogenesis of psoriasis.

Keywords: Skin Diseases; Psoriasis; Non-coding RNA; Micro RNA

INTRODUCTION

Psoriasis is a common skin disease that affects 1-3% of population. This systemic, chronic, autoimmune disease is characterized by raised and scaly skin lesions. There are five types of psoriasis: the most common type of psoriasis, that accounts for approximately 90% of cases is plaque psoriasis (psoriasis vulgaris); eruptive psoriasis (guttate psoriasis); inverse psoriasis; pustular psoriasis; and erythrodermic psoriasis [1]. Pathogenesis of the disease is associated with abnormal regulation of the immune system as a result of genetic and environmental factors, and evidence for the important role of micro RNAs (**miRNAs**) in the pathogenesis of inflammatory skin disorders is rapidly accumulating [2–6].

MicroRNAs, a class of small non-coding RNAs, were first described in 1993 when Lee et al. found *lin-4*, a developmental timing regulator in nematode *Caenorhabditiselegans* [7]. miRNAs are approximately 22-nucleotide-long, endogenous RNAs that negatively modulate gene expression by binding to the 3' untranslated region (UTR) of target messenger RNAs (**mRNAs**) [8,9]. Recent experiments have shown that target mRNAs are also repressed by miRNA-binding sites in the 5' UTR as well as in the open reading frame (**ORF**) [10, 11]. Hafner et al. found that nearly 50% of the binding sites correspond to coding sequences [12]. To date, 2588 mature miRNAs have been registered in humans (miRBase release 21) [13]. Studies suggest that over 60% of human protein-coding genes are conserved targets of miRNAs, making them one of the most abundant classes of gene-regulators [14].

miRNA Biogenesis and Mechanism of Action

MicroRNA biogenesis begins with transcription of the genomic DNA by RNA polymerase II resulting in 100 to 1000 nucleotide-long primary miRNAs (**pri-miRNAs**), followed by endonucleolytic cleavage by Drosha that results in a 70 nucleotide-long precursor miRNA (pre-miRNA) [15]. After transport from the nucleus to the cytoplasm by the Exportin-5, RNase III Dicer processes pre-miRNA stem-loop into mature double-stranded miRNA. The 'passenger strand' is degraded by endonuclease Argonaute, while the remaining so called 'guide strand' is incorporated into RNA-induced silencing complex (**RISC**) to form a functional miRNA ribonucleoprotein complex, which serves as a functional, mature miRNA [15,16]. MicroRNA–RISC complex has two mechanisms of action: 1) when miRNA is almost perfectly complementary with 3' UTR region of target mRNA deadenylation and degradation of the target mRNA occurs; 2) when miRNA is only partially complementary to its target mRNA translational inhibition occurs [17]. Moreover, one miRNA can regulate many different mRNAs and one mRNA can be regulated by more than one miRNA [14,18]. According to some literature, one miRNA could influence as many as 200 predicted target genes [19]. Some miRNAs with major sequence similarities are categorized in miRNA families and are often encoded in close proximity within the genome [20,21].

miRNAs in Skin and Skin Diseases

Human skin is the largest and probably the most complex organ, with at least five different cell types contributing to its structure. It functions as a protective barrier of the body, defending it from environmental influences and protecting the body against the loss of endogenous substances [22,23]. A vital property of skin is to locally recognize, discriminate and integrate various signals, and to immediately launch appropriate responses [24]. The skin has developed several mechanisms that include innate and adaptive immune system of the skin as well as its local steroidogenic activities to protect the body against the environment and biological factors and to maintain local homeostasis [25]. MicroRNAs were found to be implicated in key aspects of epidermal and hair-follicle development and function, as well as in autoimmune and chronic inflammatory diseases affecting skin [26,27]. Distinct miRNA families were found to be differentially expressed in the cells of epidermal and hair follicle lineages. While miR-199 family is exclusively expressed in the hair follicle, miR-200 and miR-19/miR-20 families are preferentially expressed in the epidermis [7]. A profound effect of miRNAs on epidermal and hair development was demonstrated in a functional study on Dicer and Dgcr8 conditional knockout (**cKO**) animal models. Both mutants showed indistinguishable defects in embryonic skin development. Morphological examination of Dicer and Dgcr8 cKO skin at the ultrastructural level revealed hair germ evagination, melanin granules and abnormal apoptosis [28]. Several miRNAs involved in skin development and homeostasis were already identified. Transcriptional repression of miR-34 contributes to p63 mediated cell cycle progression and expression of cyclin D1 and Cdk4 in epidermal cells [29]; miR-203 inhibits cell proliferation by repressing p63 and regulate the transition from basal to suprabasal layer in epidermis [30,31]; miR-125b expressed in skin stem cells balances self-renewal and early lineage commitment [32]; miR-200 and miR-205 are transcriptional repressors of E-cadherin [33,34]. Interest in miRNAs as possible therapeutics in dermatology is increasing, as numerous studies highlighted their importance in regulating mammalian skin development and function. Numerous studies have indicated that miRNAs play an important role in the pathogenesis of different skin diseases such as psoriasis, atopic dermatitis and malignant melanoma [35].

As discussed before, miRNAs modulate more than half of mammalian mRNAs, and a large number of miRNAs have already been confirmed to regulate cellular behavior and contribute to the pathogenesis of skin diseases [35–37]. Results of several studies indicated the clinical potential of miRNAs and proposed their uses as diagnostic biomarkers, as well as possible therapeutic targets in skin diseases [38,39]. Differences in expression of miRNAs involved in the skin's immune system have been reported for several inflammatory skin diseases including miR-21, miR-29, miR-142-3p, miR-146a, miR-150, miR-155, miR-181, miR-210 and miR-223 [3,35].

miRNAs in Psoriatic Skin

MicroRNAs have several important functions in the immune system as well as in keratinocytes. In addition to their functions in cells of the immune system, miRNAs were found to regulate

proliferation, differentiation and the production of inflammatory mediators in keratinocytes, key players in the immune response in skin [2]. Implication of miRNAs in psoriasis was first reported in a study by Sonkoly et al. where different miRNA expression profiles were observed in psoriasis-affected skin compared with healthy human skin and atopic dermatitis affected skin [4]. More than 250 miRNAs, found in peripheral blood or involved psoriatic skin, have already been reported as aberrantly expressed in psoriasis tissue [40]. miRNAs most strongly implicated in the immunopathogenesis of psoriasis are summarized in Table 1.

Table 1: Summary of aberrantly expressed miRNAs in psoriasis and their function in skin.

| miRNA | Expression | Function | References |
|--------------------|------------|---|------------------|
| miR-21 | ↑ | Regulation of keratinocyte proliferation, inflammation, T-cell apoptosis, and angiogenesis | [4,40,46,58–60] |
| miR-31 | ↑ | Regulation of keratinocyte differentiation, NF-κB activity, angiogenesis, and leukocyte migration to the skin | [59,40,54,55,61] |
| miR-99a | ↓ | Regulation of keratinocyte proliferation and differentiation | [40,35,43] |
| miR-125b | ↓ | Regulation of keratinocyte proliferation/differentiation and inflammation | [40,62,63] |
| miR-125b | ↓ | Regulation of keratinocyte differentiation and proliferation, and TNF α and other pro-inflammatory cytokines | [62–65] |
| miR-135b | ↑ | Regulation of keratinocyte differentiation and proliferation | [40,66] |
| miR-136 | ↑ | Regulation of TGF-β1-induced keratinocyte proliferation arrest | [67,40] |
| miR-138 | ↑ | Regulation of the Th-1/Th-2 balance in CD4 ⁺ T cells | [40,68] |
| miR-146a | ↑ | Regulation of hematopoietic development, inflammation, immune cell mediators, and keratinocyte proliferation | [40,45,35,69] |
| miR-155 | ↑ | Regulation of hematopoietic development and inflammation | [40,35] |
| miR-184 | ↑ | Regulation of posttranscriptional modification of mRNA and miRNA biogenesis via the miRISC complex | [40,50] |
| miR-203 | ↑ | Regulation of inflammation, STAT3 signaling, and keratinocyte proliferation/differentiation | [4,30,40,43,45] |
| miR-210 | ↑ | Regulation of regulatory T cells and their cytokine production | [40,35,51] |
| miR-221 miR-222 | ↑ | Regulation of keratinocyte and immune cell proliferation | [40,61,70] |
| miR-424 | ↑ | Regulation of keratinocyte proliferation | [40,55,43] |

Abbreviations: NF-κB nuclear factorκB; STAT3, signal transducer and activator of transcription 3; TGF- β1, transforming growth factor- β1; miRISC, miRNA-induced silencing complex; ↑: up-regulated; ↓: down-regulated.

Koga et al. reported significantly decreased serum levels of miR-125b, miR-146a, miR-203 and miR-205 in psoriasis patients compared with normal subjects [41]. MicroRNA miR-146a, a crucial negative regulator of inflammation, autoimmunity, and the innate immune response is one of the most highly up regulated miRNAs in both psoriatic skin and in the peripheral blood mononuclear cells. A strong positive correlation between increased miR-146a and IL-17, an important cytokine in the psoriasis pathogenesis, was reported [40]. Psoriasis lesions are characterised by thicker and disorganized suprabasal layer, where large amounts of keratins 6/16/17 are induced in response to trauma. Moderate up regulation of miR-203 and miR-205 were observed, and 5-fold up regulation of miR-135 in psoriatic-involved vs. normal epidermis was reported. Epidermis of affected skin contains miR-142 and miR-223, miRNAs specific to immune cells. Profiling, using

next-generation sequencing, identified 125 (90 up regulated vs. 35 down regulated) miRNAs (canonical, noncanonical miRNAs and 5'-isomiRs) with more than two fold differential expression in psoriatic skin [42]. Several other studies also reported dysregulation of miRNA-203 in patients with psoriasis [43–45]. Its importance in skin morphogenesis and differentiation of keratinocytes was confirmed by Yi et al. demonstrating its upregulation in keratinocytes that resulted in inhibition of a key regulator of basal cell “stemness” [31].

Ichihara et al. analysed tissue miRNA and identified several over expressed or suppressed miRNAs specifically in psoriasis. Significantly decreased level of miR-424 in psoriasis skin *in vivo* was observed, compared with normal skin, suggesting that *in vivo* down regulation of miR-424 is specific to psoriasis skin and could play a key role in the pathogenesis of the disease. Protein expression of predicted target genes of miR-424, MEK1 (mitogen activated protein kinase kinase 1) and cyclin E1 - two important regulators of cell proliferation, was subsequently increased in psoriatic skin [46]. Løvendorf et al. also demonstrated a characteristic miRNA signature of blood from patients with psoriasis, among them significantly upregulated miR-223 and miR-143 in the peripheral blood mononuclear cells (PBMCs) from patients with psoriasis compared with healthy controls, may serve as novel biomarkers for disease activity [47]. Recent study of Løvendorf et al. identified 13 deregulated miRNAs in psoriatic plaque epidermis compared to normal psoriatic epidermis. Three of those miRNAs: miR-181a, miR-26a, and miR-26b are also down regulated in malignant melanoma [48,49], indicating their role in the hyper proliferation, a characteristic present in both pathologies. Given their abundance of these miRNAs they could play a significant regulatory function in psoriatic skin [40].

Three other miRNAs that were up regulated in psoriasis are miR-184, miR-210 and miR-31. miR-184 may have a unique role in keratinocytes by directly dysregulating the expression of other miRNAs and targeting ARO2, a key protein involved in the RNA-induced silencing complex [50]. Overexpression of miR-210 was shown to induce immune dysfunction via targeting in CD4(+) T cells of psoriasis vulgaris by targeting FOXP3 [51]. Another miRNA whose increased values were found to contribute to skin inflammation in psoriasis is miR-31 [52–54]. A study, conducted by Xu et al. demonstrated significant overexpression of miR-31, one of the most highly overexpressed microRNAs in psoriasis skin, modulates inflammatory cytokine and chemokine production in keratinocytes by targeting serine/threonine kinase 40 (STK40) in keratinocytes and causes enhanced leukocyte migration into the skin [55].

Metalloproteinases, enzymes involved in numerous cellular activities such as cell proliferation and inflammation, were found to be altered in psoriasis tissue [56]. Because miR-221 and miR-222 target metalloproteinase inhibitor 3 (TIMP3) in psoriatic skin, Zibert et al. proposed they are fine tuners of psoriasis pathogenesis [44]. Another miRNA that targets TIMP3 and is up regulated in epidermal lesions of patients with psoriasis is miR-21. Guinea-Viniegra et al. demonstrated that its inhibition alleviated disease pathology in patient-derived psoriatic skin xenotransplants in mice

and in a psoriasis-like murine model, and suggested this mechanism as a potential therapeutic option [57]. The potential role of miR-21 as a therapeutic target was further substantiated by Meisigen et al., reporting increased apoptosis rate of activated T cells upon its inhibition [58].

From the total of 14 miRNAs most strongly implicated in the immunopathogenesis of psoriasis, reviewed in a recent study by Hawkes et al [40]. Five of them (miR-136, miR-146a, miR-155, miR-221 and miR-424) were found to have polymorphism within their seed region, a key binding location for translational suppression in the mature miRNA sequence. Because base pairing between the target mRNA and the seed region is required, these class of noncoding RNAs provides important opportunities for development of novel microRNA based therapies [71].

CONCLUSIONS

Numerous studies reported dysregulated miRNA profiles in psoriasis tissues. As novel associations for miRNAs in psoriasis and in particular miRNA - target interaction involved in the psoriasis pathogenesis are identified, the relevance of miRNAs as biomarkers and potential therapies in skin disease increases. Recent studies and first clinical trials, using microRNA based therapies (miRNA antagonists or miRNA mimics) in the treatment of various cancers, show promising results and confirm the potential of miRNAs as therapeutics. Their use is further substantiated by the fact that they are “natural” molecules produced in human body that can target multiple genes from the same pathway and can regulate multiple levels in the same pathway. Understanding the nature of miRNAs regulatory interactions with inflammatory pathways and apoptosis, as well as with other pathways, has enormous potential to grant an inside in the mechanisms and key players involved in the pathogenesis of psoriasis and contribute to the development of future miRNA based therapies.

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