

Involvement of microRNAs in skin disorders: A literature review

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ABSTRACT

Background: miRNAs are a class of noncoding RNA molecules that modulate gene expression after transcription. It is known that miRNAs are involved in various cellular processes of both normal and diseased skin. Recently, differential expressions of miRNAs have been reported and associated with several immunologic and inflammatory disorders, which indicate a common role in fundamental biologic processes.

Objective: To collect and review data from the literature on involvement of miRNA in inflammatory skin disorders.

Methods: A bibliographic search of scientific literature was carried out independently by two researchers in scientific data bases and search engines. The MeSH terms used were the following: "microRNAs" combined with "skin," "dermatitis," "urticaria," "eczema," "hypersensitivity." All research articles from inception until April 2016 were considered.

Results: A total of 11 research articles on the study of miRNAs in inflammatory skin disorders (atopic dermatitis, delayed-type hypersensitivity, eczema, toxic epidermal necrolysis) were identified. All the studies confirmed the main role of endogenous noncoding RNAs in diseases such as atopic dermatitis, allergic contact dermatitis, eczema, and toxic epidermal necrolysis.

Conclusion: The miRNAs seem to influence regulatory mechanisms of inflammation in both inducing and contrasting acute and chronic skin inflammation. They also seem to be useful instruments in identifying and staging diseases such as dermatitis and other inflammatory skin diseases. Also, the potential application of miRNAs in genetic therapies demonstrated its efficacy on animal models.

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miRNAs represent a large family of endogenous noncoding RNAs that comprise a fundamental layer of posttranscriptional regulation of gene expression. The miRNAs are small, endogenous, noncoding, single-stranded RNAs, generally 22 nucleotides long, that bind to complementary sequences of their target messenger RNA (mRNA) within the 3' untranslated region. Recently, it was established that miRNAs are powerful regulators of gene expression. Genome-wide transcriptional analyses estimated that most transcribed mammalian genomic sequences are noncoding RNAs.¹ The miRNAs negatively regulate protein expression at the posttranscriptional level through reduction of mRNA stability and inhibition of translation

(Fig. 1).² Also, miRNAs have been implicated in immune response, DNA repair, neural development, apoptosis, oxidative stress, and cancer.

First identified in *Caenorhabditis elegans* in the early 1990s, miRNAs have since been reported in a wide variety of organisms, which indicates the extreme evolutionary conservation of individual miRNA sequences. The miRNA genes are conserved and located within the introns or exons of protein-coding genes. They are transcribed in much the same way as protein-coding genes. Primary transcripts of miRNAs are generated by RNA polymerase II and sequentially processed by Ribonuclease III class enzymes.³ This processing of pre miRNAs produces an miRNA precursor of ~70 nucleotides and a mature double-stranded miRNA of 19–24 nucleotides. The mature miRNAs bind to their target sequences, are often located in the 3'-untranslated region of the mRNA, which has a partial base pair complementarity with the miRNA sequence.

One strand of this mature miRNA duplex, termed the guide strand, associates with the RNA-induced silencing complex. On incorporation into the RNA-induced silencing complex, the other strand is unwound from the guide strand and degraded, but, in some cases, both strands of the miRNA duplex are functional.⁴ The miRNA-RNA-induced silencing complexes interact with mRNA targets through partial sequence comple-

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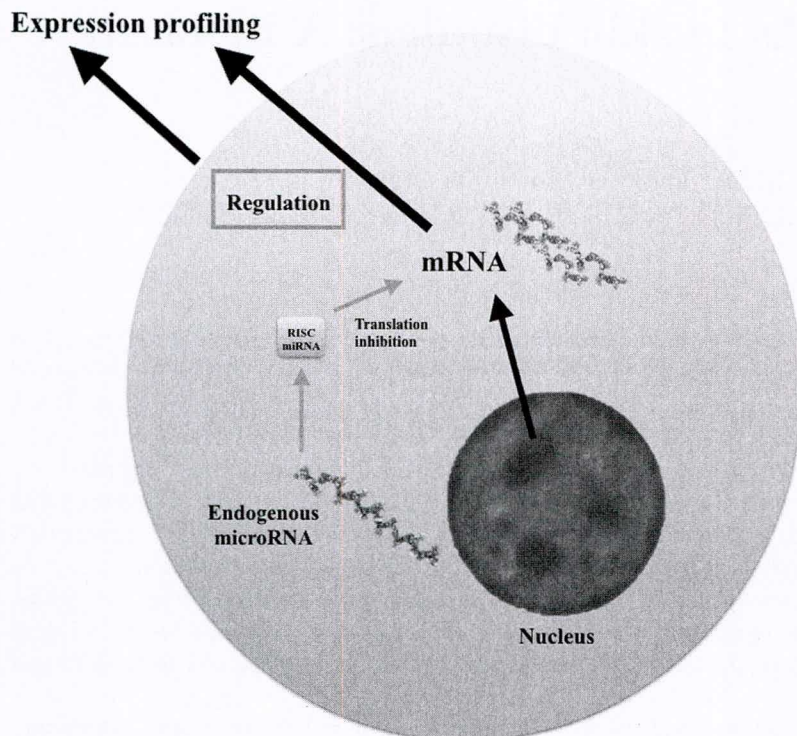


Figure 1. Endogenous *miRNA* regulate protein expression at the posttranscriptional level through reduction of messenger RNA (mRNA) stability and inhibition of translation (ribonucleoprotein complexes, i.e., RNA-induced silencing complex [RISC]) are fundamental for this phase).

mentation, typically within the 3' untranslated region of target mRNAs.⁵ Also, *miRNAs* have been implicated in immune response, neural development, DNA repair, apoptosis, proliferation, differentiation, and oxidative stress response.⁶ Recently, *miRNAs* roles in morphogenesis, wound healing, differentiation, cancer, atopic dermatitis (AD), and psoriasis have been elucidated.⁷⁻¹⁰ The aim of this study was to collect and review data from the literature on the involvement of *miRNAs* on skin disorders.

METHODS

A bibliographic search of scientific literature was carried out independently by two researchers (C.M., C.M.) in the following scientific data bases and search engines (PubMed, Embase, Medline, Web of Science, Scopus, and Google Scholar). The MeSH terms used were the following: "microRNAs" combined with "skin," "dermatitis," "urticaria," "eczema," and "hypersensitivity." Also, a simple search was conducted, and the key words used were the following: *miRNA*, and *microRNA*, each combined with skin, skin disorders, AD, dermatitis from inception until April 2016. We decided to include in our analysis all research articles published in peer-reviewed scientific journals that describe involvement of *miRNAs* with skin disorders. From the eligible articles, two researchers (C.M., C.M.) independently extracted data by using a standard data extraction form. A total of 420 records were identified through data base searching, with 2 additional records identified through other sources. Of

these, 410 were removed based on title or language. A total of 12 abstracts were screened and, after this process, one further article was excluded. Also, 11 full-text articles were assessed for eligibility and were included in the review.

RESULTS

As summarized in Table 1, a total of 11 research articles of the study of *miRNAs* in inflammatory skin disorders were identified. As mentioned in the Methods section, we decided to include only experimental studies from inception to April 2016 to provide a more-recent perspective about the role of endogenous non-coding RNAs in diseases such as AD, allergic contact dermatitis, eczema, and toxic epidermal necrolysis (TEN).

Drug-Induced Cutaneous Reactions

TEN is a severe drug-induced cutaneous reaction. Although one of the primary histologic features of TEN is keratinocyte apoptosis, its exact mechanism remains unknown. Allergic drug eruptions are divided into several clinical types, including maculopapular-type, lichenoid-type, and fixed-drug eruptions. Erythema multiforme is also known to be a common type of drug eruption; the minor form is mild and self limited, whereas the major form is accompanied by systemic symptoms and sometimes becomes severe and life threatening.¹¹

Table 1 Research articles concerning the study of *miRNAs* in inflammatory skin disorders

Study	Disease	MiRNA	Study Population (no. patients)	Age/Sex	Samples	Results
Sonkoly <i>et al.</i> , ⁷ 2010	AD	miR-155	Humans (18)	n.r.	Skin	Overexpressed
Lv <i>et al.</i> , ²² 2014	AD	miR-116, miR-255	Humans (30 children)	n.r.	Serum, urine	Upregulated miR-483-5p in serum; downregulated miR-203 in urine
Ralfkiaer <i>et al.</i> , ²⁵ 2014	AD	Multiple miRNAs	Humans (20)	n.r.	Skin	Mycosis fungoides vs patients with AD showed 21 upregulated and 17 downregulated miRNAs
Rebane <i>et al.</i> , ²³ 2014	AD	miR-146a	Humans (n n.r.)	n.r.	Skin	Upregulated
Yoon <i>et al.</i> , ²⁶ 2011	AD therapy	CCL22 miRNA	Atopic mice	n.r.	Mammalian cells	CCL22 miRNA for the <i>in vivo</i> knockdown of CCL22
Ma <i>et al.</i> , ²¹ 2015	AD	miR-155	Humans (33)	6–18 y/18 boys, 15 girls	Skin	miR-155 expression increased
Vennegaard <i>et al.</i> , ²⁸ 2012	Delayed-type hypersensitivity	Multiple miRNAs	Humans (6)	35–38 y/n.r.	Skin	Upregulation of miR-21, miR-142-3p, miR-142-5p, and miR-223
Gulati <i>et al.</i> , ²⁷ 2015	Delayed-type hypersensitivity	Multiple miRNAs	Humans (7)	20–55 y/5 men, 2 women	Skin	127 miRNAs significantly deregulated (top upregulated: hsa-miR-223, hsa-miR-150, hsa-miR-21, hsa-miR-142-5p, hsa-miR-142-3p, hsa-miR-7-2, hsa-miR-7-1, hsa-miR-7-3, hsa-miR-503, hsa-miR-150)
Saaf <i>et al.</i> , ²⁴ 2013	Eczema	miR-155 polymorphisms	Humans (1514)	n.r.	Skin	<i>BIC-miRNA-155</i> transcript increased in eczema skin
Ichihara <i>et al.</i> , ¹² 2014	Toxic epidermal necrolysis	miR-18a-5p	Humans (8 serum, 4 skin)	n.r.	Skin, serum	miR-18a-5p level increased in the skin and in the serum
Sato <i>et al.</i> , ¹³ 2015	Toxic epidermal necrolysis	miR-124	Humans (7 serum, 4 skin)	n.r.	Skin, serum	miR-124 in serum significantly higher; miR-214 increased in the skin

miRNA = MicroRNA; AD = atopic dermatitis; n.r. = data not reported; CCL = chronic lymphocytic leukemia; hsa = human; BIC = B-cell integration cluster.

Ichihara *et al.*,¹² investigated the role of *miRNAs* in the pathogenesis of severe drug eruptions. To identify pathogenic *miRNAs*, polymerase chain reaction array analyses were performed. The study demonstrated the role of the miR-18a-5p-B-cell lymphoma/leukemia-2-like protein 10 pathway in keratinocyte apoptosis and its involvement in the pathogenesis of TEN. Patients with TEN showed an increase in the miR-18a-5p level. In an *in vitro* study, transfection of the miR-18a-5p resulted in increased apoptotic cells and caspase-9 activity, which were also upregulated in the skin of patients with TEN. Moreover, miR-18a-5p mimics down-regulation of the expression of B-cell lymphoma/leukemia-2-like protein 10. Furthermore, protein and mRNA expressions of cell lymphoma/leukemia-2-like protein 10, an anti-intrinsic apoptotic molecule, were decreased in the skin of patients affected by TEN. Levels of miR-18a-5p were correlated with areas of skin erythema or erosion in patients with drug eruptions. Also, miR-18a-5p expression was correlated with the severity of drug eruptions.

Another finding regarding the upregulation of miR-124 as a marker of TEN was reported by Sato *et al.*¹³ Serum samples were obtained from 7 patients with TEN, 5 patients with Stevens Johnson syndrome, 11 patients affected by erythema multiforme, and 21 healthy subjects. The expression of miR-124 was found to be increased in the patients with TEN, Stevens Johnson syndrome, and erythema multiforme compared with the control group. Moreover, a correlation between serum miR-124 levels and clinical symptoms of TEN was considered as well as a link among the miR-124 concentration, erosion area, and SCORE of Toxic Epidermal Necrosis (SCORTEN).¹³

AD

AD is a common, chronic, relapsing, inflammatory skin disease that usually occurs in early infancy but can also start or persist in adulthood. The pathogenesis of AD has been attributed to a complex interaction, including environmental factors, host susceptibility genes, altered skin barrier function, and a deregulated immune system.¹⁴ Differential expression of *miRNAs* in several immunologic and inflammatory disorders has been shown.¹⁴ The main *miRNA*, miR-155, is linked to inflammation and immunity because of its potent upregulation in multiple immune cell lineages, including lymphocytes, fibroblasts, mast cells, macrophages, and dendritic cells implicated in the pathogenesis of chronic skin inflammation.¹⁵⁻²⁰

A differential expression of miR-155 in the peripheral circulation and lesional skin from patients affected by AD was proposed by Ma *et al.*²¹ A possible regulatory effect of miR-155 on the differentiation and function of T-helper (Th) type 17 cells has also been investigated.

Patients with acute AD should not be treated with systemic glucocorticoids, immunosuppressive agents, or desensitization therapy 6 months before the start of the study or with local glucocorticoids or calcineurin inhibitors the week before. Samples of skin tissue were collected from 15 patients with AD, and samples of normal skin were obtained from 15 healthy subjects with no history of atopic disorders or inflammatory skin diseases. Analysis of the results showed a higher expression of miR-155 in both AD peripheral CD4 T cells and skin specimens. A comparison of miR-155 expression levels between AD peripheral CD4T cells and AD disease severity, had revealed a relatively positive correlation. An increased Th17 cell percentage in peripheral CD4T, an enhanced expression of RAR-related orphan receptor γ thymus and interleukin 17 (IL-17) mRNA in peripheral CD4 T cells, lesional skin, and perilesional skin, and an elevated concentration of IL-17 in plasma in AD, have been shown. Moreover, a decreased Suppressor of cytokine signaling 1 expression was confirmed in AD peripheral CD4 T cells and plasma concentrations as well as in lesional and perilesional skin.²¹

To assess new biomarkers for AD, Lv *et al.*,²² performed genome-wide *miRNA* profiling in serum and urine in 30 children affected by the disease and in 28 healthy children; 116 *miRNAs* in urine and 255 *miRNAs* in serum have been detected. The researchers showed that serum miR-203 and miR-483-5p were significantly up-regulated in children with AD compared with the control group, whereas miRNA-203 was significantly downregulated in urine from patients with AD.²² Moreover, with the aim to evaluate the link between *miRNA* expression and inflammatory response, global inflammatory factors were detected in serum. Analysis of the results indicated that the upregulation of miR-203 in serum was significantly associated with soluble tumor necrosis factor receptor I and soluble tumor necrosis factor receptor II expression.²²

On the basis that chronic skin inflammation in AD keratinocytes is linked to elevated expression of proinflammatory genes and to the activation of innate immune responses, Rebane *et al.*,²³ investigated the role of miR-146a in AD skin inflammation. An *miRNA* expression profiling of cultured primary keratinocytes was performed in healthy individuals and patients affected by AD. Analysis of the results indicated that 12 *miRNAs* were differentially expressed in keratinocytes. Among these *miRNAs*, miR-146a was the second-most strongly upregulated after miR-10b. Analysis of the results demonstrated an increased level of miR-146a in keratinocytes of patients with AD and during AD skin inflammation. This increased expression regulates chronic inflammatory processes triggered by interferon γ (IFN γ) and activation of nuclear factor κ -light-chain-enhancer of activated B cells. To

investigate the miR-146a role in skin inflammation, a mouse model of AD has been considered. Analysis of the results indicated that stronger inflammation with an increased accumulation of infiltrating cells in the dermis was produced in miR-146a-deficient mice. Moreover an elevated expression of interferon, chemokine (C-C motif) ligand 5 (CCL5), CCL8, and ubiquitin D in skin, and IFN γ , IL-1b, and ubiquitin D in draining lymph nodes was observed.²³ Ichihara *et al.*¹² in their study also took in analysis 4 patients with AD and reported that there were 11 *miRNAs* up- or downregulated compared with healthy controls (hsa-miR-9-5p, hsa-miR-18a-5p, hsa-miR-191-3p, hsa-miR-223-3p, hsa-miR-298, hsa-miR-346, hsa-miR-383, hsa-miR-424-3p, hsa-miR-495-3p, hsa-miR-605, hsa-miR-1908).

Sonkoly *et al.*⁷ analyzed *miRNA* expression in punch biopsy specimens from healthy subjects and from patients with AD with house-dust mite allergy who underwent AD patch testing. Another AD group of patients underwent staphylococcal enterotoxin B patch tests. A global *miRNA* profile for 365 human *miRNAs* was performed. Forty-four *miRNAs* were significantly differentially expressed in AD lesions compared with healthy skin. One of the highest-ranked upregulated *miRNAs* was miR-155. The researchers found that miR-155 was significantly upregulated in AD lesions. To obtain further data regarding the function of miR-155 in the skin, a quantification of expression in skin and in organs and tissues of healthy subjects was performed. Analysis of the data obtained showed that miR-155 expression was higher in the thymus, spleen, and lung. Lower miR-155 levels were found in healthy skin compared with other organs. Moreover, miR-155 is regulated by T-cell activation signals *in vitro*, and it could be considered an important trigger factor of AD *in vivo*. In conclusion, the researchers indicated that miR-155 is involved in the regulation of T-cell responses through a suppression of cytotoxic T-lymphocyte antigen 4 and by enhancing T-cell proliferation.⁷

Saaf *et al.*,²⁴ performed a large-scale gene-expression study to evaluate the association between miR-155 and eczema susceptibility. It was found that the B-cell integration cluster (BIC) transcript is consistently overexpressed in eczematous skin compared with healthy subjects skin. Moreover, the researchers demonstrated that BIC expression was induced by the application of *Malassezia sympodialis* to nonlesional skin of patients with eczema. Because BIC transcript maps to an asthma and eczema susceptibility region on chromosome 21q21, the researchers investigated the BIC-miR-155 association with eczema susceptibility. A genotype of five single-nucleotide polymorphisms, which tagged the BIC/miR-155 chromosomal region, was performed in a eczema cohort of 1514 Swedish individuals, which consisted of 406 multiplex eczema families. Analysis of

the results indicated a not statistically significant trend of association of the BIC gene with atopic eczema. The researchers indicated that miR-155 is highly expressed in lesional skin and in *M. sympodialis* patch-tested nonlesional skin of patients with eczema in comparison with the controls but not proving an association between BIC/miR-155 gene and atopic eczema.²⁴

Ralfkiaer *et al.*²⁵ tried a better determination of *miRNAs* role in AD by comparing AD *miRNAs* profile to the one of a similar pathology for clinical, histologic, and immunologic aspects (early mycosis fungoides). They studied the *miRNA* expression in 13 patients with early mycosis fungoides and in 20 subjects with AD, and found that 38 *miRNAs* were differentially expressed in patients with early mycosis fungoides versus patients with AD. Yoon *et al.*,²⁶ developed a genetic therapy by using bacterial *miRNA*. They reproduced a CCL22 *miRNA* and used it in mice to obtain an *in vivo* knock-down of CCL22, a macrophage chemokine involved in Th 2 associated skin inflammatory lesions. By treating mice with skin lesion AD-like is skin lesion atopic dermatitis like, they noticed the inhibition of IL-4 and the augmentation of IFN γ , together with the suppression of CCL22 levels.

Delayed-Type Hypersensitivity Reaction

Delayed-type hypersensitivity reaction is defined as an inflammatory reaction mediated by T cells and monocytes and/or macrophages rather than by antibodies. Gulati *et al.*²⁷ performed a global *miRNA* expression profile of skin in seven subjects sensitized to diphenylcyclopropenone (DPCP). After desensitization, two challenge applications of DPCP or placebo applications were performed. Three and 14 days after challenge, punch biopsies specimens were taken and a further biopsy of the DPCP-treated site was performed 120 days after challenge. The *miRNA* expression profiles were performed through barcoded small RNA sequencing after RNA extraction. Analysis of the results indicated that, in DPCP-challenged skin, 127 *miRNAs* were significantly deregulated 3 days after challenge. After 14 days, 43 *miRNAs* were deregulated, and 6 *miRNAs* were upregulated 120 days after challenge. The researchers indicate that an upregulation of *miRNAs* miR-21, miR-142-3p, miR-142-5p, and miR-223 at 3 and 14 days after challenge.

Vennegaard *et al.*,²⁸ investigated *miRNA* expression in allergic contact dermatitis in humans and mice. In human study, six subjects were sensitized with DPCP on the skin of the buttocks. Total RNA was isolated from six 10- μ m frozen-tissue specimens. In sensitized subjects, no signs of inflammatory response in the site challenged with vehicle, was seen. All the subjects sensitized to DPCP had visible signs of allergic contact dermatitis at the DPCP-challenged site, from mild mac-

ular erythema to strong erythematous reaction. Microarray analysis showed that there were significant differences in the expression of a great number of *miRNAs* between challenge and vehicle sites. Analysis of the results showed that, in allergen-challenged skin, four *miRNAs* (miR-21, miR-223, miR-142-3p, and miR-142-5p) were upregulated. In a mouse model, the mice were either exposed to 2,4-dinitrofluorobenzene for three consecutive days on both ears, followed by challenge 21 days later or were only exposed to 2,4-dinitrofluorobenzene once. When comparing *miRNA* expression induced by allergic contact dermatitis in humans with that induced by allergen in mice, 11 of the 20 most-modified human *miRNAs* had a mouse orthologue.²⁸

DISCUSSION

As shown in previous reports, *miRNAs* are involved in the pathogenesis of multiple disorders, from wound healing to cancer to psoriasis *etc.*^{8–10} Many researchers focused on the demonstration of involvement of *miRNAs* in skin inflammation. Sonkoly *et al.*,⁷ by analyzing skin lesions of patients affected by AD, found a high expression of miR-155 and showed that it increased the proliferative response of CD4⁺ T cells by downregulating cytotoxic T-lymphocyte antigen 4 expression. Yoon *et al.*²⁶ suppressed the CCL22 chemokine, linked to Th2-associated skin inflammation, by downregulating the CCL22 gene with CCL22 *miRNA* administration. Skin samples of sensitized humans and mice had augmented levels of the other *miRNAs* in a model of induced contact dermatitis (miR-21, miR-142-3p, miR-142-5p, and miR-223 were upregulated).²⁸

Based on their previous study and because miR-155 was the only known *miRNA* derived from the BIC, Saaf *et al.*²⁴ speculated that BIC-miR-155 could be genetically associated with eczema susceptibility. This association was not confirmed. Instead, this study confirmed once more the elevation of miR-155 in lesional skin.²⁴ Another *miRNA* that exerts inhibiting effects on many proinflammatory factors was the miR-146a; its levels were reported to be higher in AD chronic skin lesions. To confirm this observation, Rebane *et al.*,²³ demonstrated that mice knocked down for miR-146a developed a stronger dermis inflammation,²³ then elevated levels of miR-155 in patients with AD were correlated with significantly higher circulating Th17 cell percentages. These data were reproduced *in vitro*, which obtained a Th17 cell percentage augmentation in CD4⁺ T cells transfected with a miR-155 mimic.²¹

The *miRNA* involvement in chronic skin inflammation, after inducing delayed-type hypersensitivity, was confirmed by the report of the upregulation of several *miRNAs* at different time points. According to data obtained by the cited authors in primis (firstly) and

then by our group, speculated that the role of *miRNAs* is not only in enhancing inflammation but also in resolving it.²⁷ Although with similar clinical, histologic, and immunologic aspects, AD and early mycosis fungoides showed very different miR profiles.²⁵ All these results seemed to confirm that some *miRNAs* are certainly involved in AD pathogenesis (*i.e.*, miR-155). In other studies,^{22,25} the upregulation of other *miRNAs* were reported, which indicated a incomplete understanding of the mechanisms in generating chronic skin inflammation. An attempt to use *miRNAs* as potential biomarkers in AD was made by dosing serum miR-203 and observed that it was more elevated in patients with AD than in controls; serum miR-483-5p was associated with AD and other atopic conditions. The same miR-203, augmented in serum, was noticeably diminished in the urine of patients with AD.²² An early therapeutic attempt was made by generating an *miRNA* able to suppress a Th2 proinflammatory chemokine often involved in AD pathogenesis, this attempt lead to the suppression of this Th2 proinflammatory cytokine and gave start to new therapeutic approaches in this skin pathology.²⁶

Although TEN can be considered an acute and not a chronic skin reaction, we decided to include it in this review because of some common aspects that involve skin inflammation and keratinocytes with the AD and delayed-type hypersensitivity dermatitis. The transfection of the miR-18a-5p mimic into keratinocytes led to an elevation of apoptotic cells and of caspase-9 activity as demonstrated in skin samples of patients with TEN. Serum levels of miR-18a-5p were significantly also higher in patients with TEN and correlated with skin eruptions.¹² An important role of *miRNAs* in TEN pathogenesis was confirmed by serum elevation of miR-124 and a high skin concentration of miR-214.¹³ Although these findings are not yet sufficient to give a complete picture of the role of this endogenous non-coding RNAs, these findings could indicate their helpful biomarker function (*i.e.*, serum miR-124 in TEN).

CONCLUSION

Larger studies are needed to investigate the regulatory mechanisms of inflammation induced by *miRNAs* that leads to the development of chronic and acute skin diseases. However, the study of these molecules could give, in clinical practice, an useful instrument in identifying and staging skin diseases with an important inflammatory base such as dermatitis, TEN, urticaria, *etc.* Dosing circulating *miRNAs* could, in the near future, be an immediate and low-cost method to monitor the course of some inflammatory diseases, following the path tracked by other emerging biomarkers (*i.e.*, serum clusterin for AD)²⁹; by following this path, circulating *miRNAs* could also be an option in monitoring

treatment efficacy and give some prognostic information. Also, once these mechanisms are clarified, another step forward should be to generate *miRNA* mimics to interfere with the course and the prognosis of inflammatory skin diseases.

REFERENCES

- Setoyama T, Ling H, Natsugoe S, and Calin GA. Non-coding RNAs for medical practice in oncology. *Keio J Med* 60:106–113, 2011.
- Felekis K, Touvana E, Stefanou Ch, and Deltas C. microRNAs: A newly described class of encoded molecules that play a role in health and disease. *Hippokratia* 14:236–240, 2010.
- Borchert GM, Lanier W, and Davidson BL. RNA polymerase III transcribes human microRNAs. *Nat Struct Mol Biol* 13:1097–1101, 2006.
- Hu HY, Yan Z, Xu Y, et al. Sequence features associated with microRNA strand selection in humans and flies. *BMC Genomics* 10:413, 2009.
- Fabian MR, Sonenberg N, and Filipowicz W. Regulation of mRNA translation and stability by microRNAs. *Ann Rev Biochem* 79:351–379, 2010.
- Fiorucci G, Chiantore MV, Mangino G, et al. Cancer regulator microRNA: Potential relevance in diagnosis, prognosis and treatment of cancer. *Curr Med Chem* 19:461–474, 2012.
- Sonkoly E, Janson P, Majuri ML, et al. MiR-155 is overexpressed in patients with atopic dermatitis and modulates T-cell proliferative responses by targeting cytotoxic T lymphocyte-associated antigen 4. *J Allergy Clin Immunol* 126:581–589.e1–20, 2010.
- Wei T, Orfanidis K, Xu N, et al. The expression of microRNA-203 during human skin morphogenesis. *Exp Dermatol* 19:854–856, 2010.
- Hawkes JE, Nguyen GH, Fujita M, et al. microRNAs in psoriasis. *J Invest Dermatol* 136:365–371, 2016.
- Ren GB, Wang L, Zhang FH, et al. Study on the relationship between miR-520g and the development of breast cancer. *Eur Rev Med Pharmacol Sci* 20:657–663, 2016.
- Harr T, and French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis* 5:39, 2010.
- Ichihara A, Wang Z, Jinnin M, et al. Upregulation of miR-18a–5p contributes to epidermal necrolysis in severe drug eruptions. *J Allergy Clin Immunol* 133:1065–1074, 2014.
- Sato S, Ichihara A, Jinnin M, et al. Serum miR-124 up-regulation as a disease marker of toxic epidermal necrolysis. *Eur J Dermatol* 25:457–462, 2015.
- Nutten S. Atopic dermatitis: Global epidemiology and risk factors. *Ann Nutr Metab* 66(suppl. 1):8–16, 2015.
- Song L, Lin C, Wu Z, et al. miR-18a impairs DNA damage response through downregulation of ataxia telangiectasia mutated (ATM) kinase. *PloS One* 6:e25454, 2011.
- Sand M, Skrygan M, Georgas D, et al. The miRNA machinery in primary cutaneous malignant melanoma, cutaneous malignant melanoma metastases and benign melanocytic nevi. *Cell Tissue Res* 350:119–126, 2012.
- Sonkoly E, Stahle M, and Pivarcsi A. MicroRNAs: Novel regulators in skin inflammation. *Clin Exp Dermatol* 33:312–315, 2008.
- Xiao C, and Rajewsky K. MicroRNA control in the immune system: Basic principles. *Cell* 136:26–36, 2009.
- Lu TX, and Rothenberg ME. Diagnostic, functional, and therapeutic roles of microRNA in allergic diseases. *J Allergy Clin Immunol* 132:3–13; quiz 14, 2013.
- Rebane A, and Akdis CA. MicroRNAs: Essential players in the regulation of inflammation. *J Allergy Clin Immunol* 132:15–26, 2013.
- Ma L, Xue HB, Wang F, et al. MicroRNA-155 may be involved in the pathogenesis of atopic dermatitis by modulating the differentiation and function of T helper type 17 (Th17) cells. *Clin Exp Immunol* 181:142–149, 2015.
- Lv Y, Qi R, Xu J, et al. Profiling of serum and urinary microRNAs in children with atopic dermatitis. *PloS One* 9:e115448, 2014.
- Rebane A, Runnel T, Aab A, et al. MicroRNA-146a alleviates chronic skin inflammation in atopic dermatitis through suppression of innate immune responses in keratinocytes. *J Allergy Clin Immunol* 134:836–847.e11, 2014.
- Saaf A, Kockum I, Wahlgren CF, et al. Are BIC (miR-155) polymorphisms associated with eczema susceptibility? *Acta Derm Venereol* 93:366–367, 2013.
- Ralfkiaer U, Lindahl LM, Litman T, et al. MicroRNA expression in early mycosis fungoides is distinctly different from atopic dermatitis and advanced cutaneous T-cell lymphoma. *Anticancer Res* 34:7207–7217, 2014.
- Yoon WS, Lee SS, Chae YS, and Park YK. Therapeutic effects of recombinant *Salmonella typhimurium* harboring CCL22 miRNA on atopic dermatitis-like skin in mice. *Exp Mol Med* 43:63–70, 2011.
- Gulati N, Lovendorf MB, Zibert JR, et al. Unique microRNAs appear at different times during the course of a delayed-type hypersensitivity reaction in human skin. *Exp Dermatol* 24:953–957, 2015.
- Vennegaard MT, Bonefeld CM, Hagedorn PH, et al. Allergic contact dermatitis induces upregulation of identical microRNAs in humans and mice. *Contact Dermatitis* 67:298–305, 2012.
- Sol IS, Kim YH, Lee KE, et al. Serum clusterin level in children with atopic dermatitis. *Allergy Asthma Proc* 37:335–339, 2016.□

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