Importance of microRNAs in skin morphogenesis and diseases

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SUMMARY

MicroRNAs (miRNAs) are small (20–22 nt), non-coding RNAs involved in post-transcriptional gene silencing. Their binding to the 3' UTR of target mRNAs influences the translation or stability of the transcripts. miRNAs have been shown to regulate several developmental and physiological processes, including stem cell differentiation and the immune response. Recent findings report their involvement in hair follicle morphogenesis (ablation of miRNAs from keratinocytes causes several defects, such as evagination instead of invagination), in psoriasis (skin-specific expression of *miR-203* and psoriasis-specific expression of *miR-146a*, *miR-21* and *miR-125b* in the skin), in autoimmune diseases affecting the skin, such as SLE and ITP, in wound healing (changes in the expression of specific miRNA at specific phases of the regeneration process), and in skin carcinogenesis (a novel miRNA signature that includes induction of *miR-21*, a candidate oncogenic miRNA). Researchers worldwide are interested in miRNAs as potential therapeutic targets (such as in the case of psoriasis) and potential diagnostic biomarkers (such as in case of SLE).

KEY WORDS

miRNA, psoriasis, SLE, hair follicle morphogenesis, skin carcinogenesis, wound healing

Introduction

miRNAs are recently discovered non-coding RNA molecules that bind to the 3' untranslated regions (UTR) of target mRNAs in a sequence specific manner in order to influence the translation or stability of the transcripts. miRNAs are small, approximately 22 nucleotides (nt) long. Bioinformatics studies on the genomes of multiple organisms suggest that this length maximizes target-gene specificity and minimizes non-specific effects (1). For detailed processing of miRNA, see Figure 1 (2, 3).

miRNA processing

miRNAs are genome encoded, derived from the intergenic regions (encoded as single gene or gene clusters) or intron regions. Through their lifecycle, miRNAs must undergo extensive post-transcriptional modification. miRNAs are transcribed with Pol II or Pol III from a RNA-coding gene. The resulting primary transcript, known as a *pri-miRNA* (with polyA tail and 7-methylguanosine cap), is processed in the cell nucleus to a 70-nt stem-loop structure called a *pre-miRNA* by the RNase III enzyme called Drosha and the double-

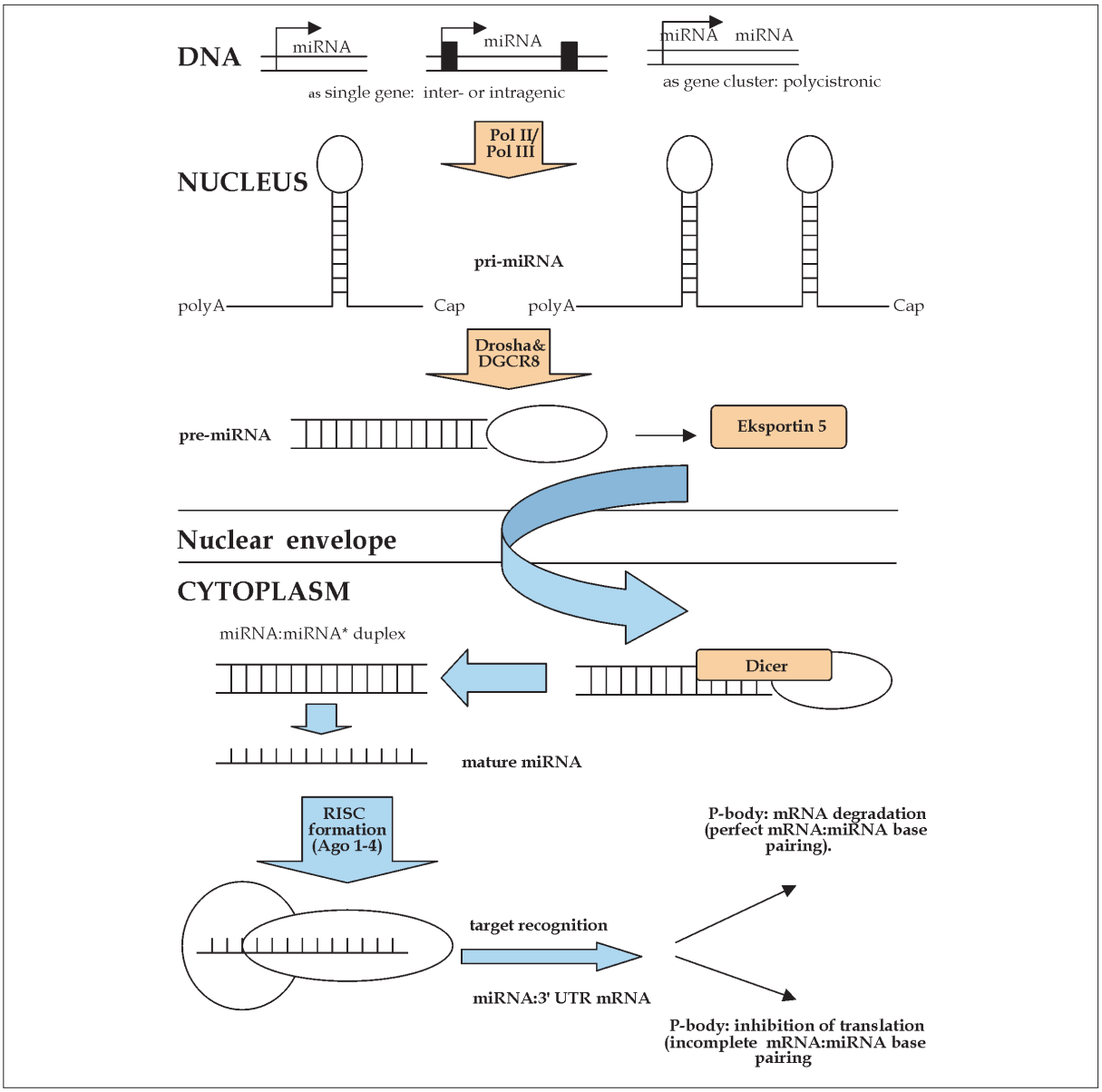


Figure 1. Schematic overview of the miRNA biogenesis pathway.

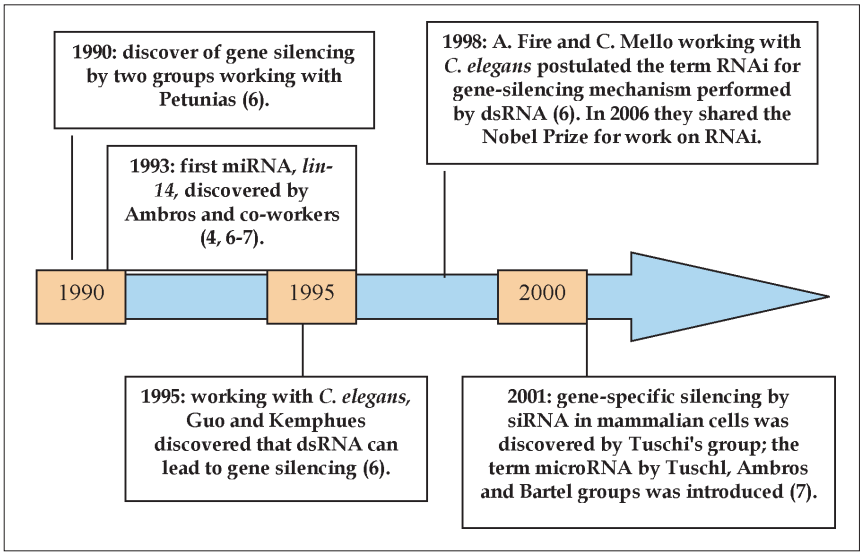
stranded (ds) RNA-binding protein, DGCR8. The resulting stem-loop structure is imported in cytoplasm by the transporter protein Exportin 5. The dsRNA portion of this *pre-miRNA* is bound and cleaved by Dicer, another RNase III enzyme, to produce the mature miRNA molecule (20–22 nt). One of the two strands of each fragment (miRNA), known as the *guide strand*, is then incorporated into the RNA-induced silencing complex (RISC) and base-pairs with complementary sequences; the other is degraded (miRNA*) (2).

RISC activation and catalysis

After base pairing between miRNA and target mRNA, degradation of the target mRNA results when complementarity is perfect or suppression of translation results when base pairing between these two molecules is incomplete. Especially in animals, miRNAs inhibit the translation of many different mRNAs without degrading the target mRNA. Argonaute proteins (Ago), the catalytic components of RISC, are localized to specific regions in the cytoplasm called P-bodies, which are regions with high rates of mRNA decay or sequestration; miRNA activity is also clustered in P-bodies (3). (4).

Recent estimations show that miRNAs regulate thirty percent of human genes. One miRNA can regulate many different mRNAs (one miRNA could influence as many as 200 predicted target genes), and one mRNA can be regulated by more than one miRNA. There are several avail-

Figure 2: Historical overview of RNAi discovery.



able programs to predict mRNA targets for specific miRNA or to predict possible miRNA binding sites for specific mRNA, but all predicted targets have to be validated in vivo. We are just at the beginning of understanding the complex miRNA:mRNA:protein network regulating cellular functions (5).

miRNA functions

The role of endogenously expressed miRNA (the first discovered miRNA was *lin-4*) in down-regulating gene expression was first described by Ambros et al. in 1993 for *C. elegans*, although the term microRNA was introduced in 2001. For a schematic historical overview, see Figure 2 (4, 6, 7).

RNA interference (RNAi) is an evolutionary conserved mechanism in response to the presence of dsRNA in the cell. The enzyme Dicer, which cleaves dsRNA to short double-stranded fragments of 20–25 base pairs, initiates the RNAi pathway. The short dsRNA fragments are known as small interfering RNAs (siRNA) with perfect complementarity to the target gene mRNA, causing its degradation. RNAi is RNA-guided regulation of gene expression, historically known by other names, including post-transcriptional gene silencing. When the dsRNA is exogenous, coming from infection by a virus with RNA genome or laboratory manipulations, the RNA is imported directly into the cytoplasm and cleaved to short fragments by the enzyme Dicer. The initiating dsRNA can also be endogenous, as in pre-miRNAs (see Figure 1), expressed from RNA-coding genes in the genome (4, 6, 7).

Recent advances in miRNA research have provided evidence of the importance of miRNAs in normal cellular function, and diseases resulting from abnormal miRNA expression profiles in diseased tissues compared to healthy tissues.

miRNAs are important in the regulation of development, especially in regulating morphogenesis and the maintenance of undifferentiated or incompletely differentiated cell types (stem cell differentiation, cardiac and skeletal muscle development, neurogenesis, hematopoiesis, etc.) (4).

They are involved in several physiological processes such as insulin secretion, cholesterol metabolism, the immune response, and heart diseases (4).

Disruptions of miRNA target interaction in the form of single-nucleotide polymorphisms (SNPs) either in the miRNA gene or its target site (3' UTR mRNA) could lead to complete gain or loss of miRNA function, thus leading to a diseased state. The assumption of miRNA target variation was confirmed in the case of Tourette syndrome and the highly muscular phenotype of Texel sheep (4–5). In contrast to the miRNA target sites in mRNA transcripts, where the potential of variation is huge, variants identified in miRNA precursor sequences tend to be extremely rare, usually restricted to one individual (5).

miRNAs are thought to be involved in carcinogenesis. A lower miRNA expression profile in cancerous compared to normal tissues suggests a role of miRNAs in the formation of tumors and regulation of the cell cycle; over-expression of miRNAs in cancer may inhibit tumor-suppressors; mutation in miRNA genes or their translocation and subsequently loss-of-function of miRNA, so that target proto-oncogenic mRNA is over-expressed, was shown to be involved in chronic lymphocytic leukemia (CLL); mutation in miRNA genes can also cause gain-of-function of miRNA, so that target mRNA is repressed leading to aberrant cell cycle and proliferation. In addition, it is estimated that 50% of miRNA genes are located at fragile chromosome sites associated with development of cancer (4).

RNAi and miRNAs in therapeutic applications

Although it is difficult to introduce long dsRNA strands into mammalian cells due to the interferon response, the use of RNAi as a therapeutic approach has been successful. Among the first applications to reach clinical trials were the treatment of macular degeneration and respiratory syncytical virus infection (8), reversal of induced liver failure in mouse models (9), antiviral thera-

pies (10), neurodegenerative diseases (11), and cancer, by silencing up-regulated genes in tumor cells or genes involved in cell division (12). A key area of research in the use of RNAi for clinical applications is the development of a safe delivery method, which to date has involved mainly viral (e.g., lentivirus, adenovirus, and adeno-associated virus) and non-viral (e.g., nanoparticles, aptamers, and stable nucleic-acid-lipid particles) vector systems similar to those suggested for gene therapy (13). Another strategy successfully tested for *in vivo* gene silencing in solid tumors is electrically mediated siRNA delivery defined as electroporation (14), also widely used for delivery of therapeutic genes such as cytokines, for treatment of various diseases (15). This application uses electric current on a living surface (as the skin or plasma membrane of a cell) in order to open pores or channels through which a biologic material may pass (as a drug or DNA). Electroporation of siRNA into pre-established tumors was also tested as a potential therapeutic intervention in malignant melanoma (16).

Using RNAi approaches, miRNAs may serve as therapeutic targets in the future. For miRNA that is under-expressed, re-introduction of the mature miRNA into the affected tissue would restore the regulation of the target gene. By contrast, over-expressed miRNA could be down-regulated by reducing the mature miRNA level through direct targeting or by reducing components of the miRNA biogenesis. The latter is possible for short-term use and under restricted conditions (17).

miRNAs in skin physiology

The majority of studies are focused on the potential role of miRNA in the development, morphogenesis, and formation of tumors. This review is focused on miRNAs' functions in skin development and physiology. Recent findings have reported miRNA involvement in hair follicle morphogenesis (miRNAs being differentially expressed in epidermis and hair follicles), and autoimmune and chronic inflammatory diseases affecting skin (psoriasis, SLE, ITP), and their roles were also proposed in wound healing and skin carcinogenesis (18–23).

Skin carcinogenesis

miRNAs are often abnormally regulated in tumorigenesis and cancers. Recent research reported a miRNA expression profile in the TGF-β-directed model of epithelial cell plasticity (from keratinocytes), which is a basic mechanism after epidermal injury and in the progression of epithelial tumors. Induction of a potential oncogenic miRNA, *miR-21*, which is associated with a majority of cancers, was of particular interest, suggesting the molecular parallel between the model of epithelial cell plasticity and carcinogenesis (TGF-β is regulator of both processes). Analysis of gene expression profiling and miRNA screening results in combination with target prediction algorithms was performed to propose miRNA:mRNA regulatory interactions and their involvement in tumor progression (18). In addition, two recent studies researched the miRNA expression profile in human melanoma cell lines, which exhibit unique expression profiles and DNA copy number alterations of miRNA genes. It is hypothesized that copy number change in miRNA may be involved in aberrant regulation of the miRNA gene in tumors (24).

Cutaneous wound healing

Tissue regeneration, wound healing, lymphocyte activation, and carcinogenesis are processes defined by the stimulation of cells to proliferate. Dermal fibroblasts are one of most important cells involved in the wound-healing process, being responsible for attracting new cells by secreting growth factors and extra-cellular proteins (25). Growth factors enhance tissue repair by chemotaxis, cell proliferation, angiogenesis, and so on. (26) To identify if the complex mixture of components in serum or a specific component alone is required to trigger the wound-healing response in skin fibroblasts, Gu et al. stimulated skin and lung fibroblasts through exposure to serum or purified growth factors. As a result, dermal fibroblasts proliferated in response not only to serum but also to individual growth factors (19, 25, 26). In addition, analysis of the potential involvement of miRNAs in regulating the transition to proliferation was performed. The obtained cluster of 33 miRNAs with similar and consistent expression profiles across the replicates (e.g., *miR-125b, miR-143, miR-21*) suggest involvement of miRNAs in regulation of expression of target genes important for the entry of fibroblasts into the cell cycle and proliferation (19).

In addition, the role of miRNAs was also proposed in a specific phase of the cutaneous wound-healing process. Repair of damaged human skin is a physiological process involving three overlapping phases: inflammation, proliferation (epithelialization, angiogenesis, granulation, and tissue formation) and maturation. Induction of the expression and/or repression of systemic and local factors of these processes are key mechanisms of the regenerative process. Shilo et al. reviewed the role of miRNAs in angiogenesis to outline the potential importance of studying miRNAs involvement in wound angiogenesis. He proposed (i) that the cutaneous wound-healing process involves changes in the expression of specific miRNA at a specific phase of wound healing, and (ii) that aberrant regulation of specific miRNA and impairments in wound angiogenesis may play a key role in the abnormal healing sequence in chronic problem wounds (20).

Table 1. Expression profile of psoriasis-associated miRNAs among different organs and cell-types (adapted from Sonkoly et al., 2007).

miRNA	Organs	Cell type	Psoriasis	Atopic eczema
miR-203	Skin-specific	Keratinocytes	Up-regulated	No change
miR-146a	All	Immune cells	Up-regulated	No change
miR-125b	All	Structural cells	Down-regulated	Down-regulated
miR-21	All	Structural and inflammatory cells	Up-regulated	Up-regulated

Note. structural cells = keratinocytes, fibroblasts; immune/inflammatory cells = lymphocytes, mast cells, granulocytes, dendritic cells, NK cells.

Psoriasis

Psoriasis is the most prevalent chronic inflammatory skin disease, with an estimated prevalence from 0.5 to 4.6%, varying by country and ethnicity. Genetic and environmental factors in connection with abnormal regulation of the immune system are thought to be involved in pathogenesis of the disease. Several different cell types (keratinocytes, fibroblasts, monocyte-derived immune cells, T cells, and mast cells) that normally occur in skin are relevant in the formation of psoriatic lesions. Keratinocytes show abnormal differentiation and proliferation because of aberrant cell signaling and production of mediators involved in immune cell activation. It is widely accepted that psoriasis is a consequence of impaired cross-talk between the immune system and the structural cells of the skin (21, 27, 28). To show a specific miRNA expression profile in psoriasis-affected skin representing leukocyte- and keratinocyte-derived miRNAs, Sonkoly et al. compared psoriasis-affected skin to atopic eczema (another chronic inflammatory skin disease) and to healthy human skin (21).

The miRNA signature in psoriasis

The psoriasis-associated miRNAs identified in the skin showed different expression profiles among 21 organs studied (Table 1). *MiR-203* was expressed more than 100-fold higher in skin compared to other organs, and at lower levels in organs with squamous epithelium, suggesting a specific function for this miRNA in the formation/function of squamous epithelia. *MiR-146a, miR-21*, and *miR-125b* were detected in all the organs studied, but their expression showed different patterns. *MiR-146a* was highly expressed in organs containing a high percentage of leukocytes and at low levels in healthy skin, suggesting expression of *miR-146a* in the skin by infiltrating cells. *MiR-125b* was expressed mostly in organs containing cells of ectodermal origin. *MiR-21* showed the highest expression in the bladder, lung, prostate, and colon (21).

Cell-type-specific miRNAs

Systematic analyses of expression of identified psoriasis-associated miRNAs in the skin (*miR-203, miR-146a, miR-21,* and *miR-125b*) and in cells present in healthy and psoriatic skin (keratinocytes, dermal fibroblasts, melanocytes, and leukocyte/immune cell subsets) showed a distinctive expression pattern in the cell types studied (similar to their expression profiles in different organs; see Table 1). *MiR-203,* which was absent in other cell types analyzed, suggests that this miRNA plays a role in keratinocyte functions in healthy and psoriasis-affected skin. In contrast, *miR-146a*, absent in keratinocytes and dermal fibroblasts, is preferentially expressed in immune cells. *MiR-125b* is expressed at lower level in inflammatory cells in comparison to structural cells (fibroblasts, keratinocytes, and melanocytes). *MiR-21* is expressed by both structural and inflammatory cells. Abnormal regulation of keratinocyte- and leukocyte-specific miRNAs in psoriasis indicates altered miRNA-mediated gene regulation that may contribute to the abnormal interactions of keratinocytes and immune cells (21).

miRNAs in psoriasis-affected skin and their target genes

Among the identified psoriasis-associated miRNAs (*miR-203, miR-146a, miR-21,* and *miR-125b*), some of the target genes for *miR-146a* have been already identified, thus Sonkoly et al. directed their research toward keratinocyte-specific *miR-203*, up-regulated in psoriasis.

TNF-alpha is one of the most important mediators in leukocyte-keratinocyte interactions in psoriasis (28). Psoriasis-specific miRNA, *miR-146a*, inhibits the expression of two regulators of the TNF-a signalling pathway, IRAK1 and TRAF6. Thus, *miR-146a* is probably involved in the pathogenesis of psoriasis by regulation of the TNF-alpha signaling in the skin (21, 29).

In psoriatic plaques, up-regulated *miR-203* was shown to be involved in down regulation of an evolutionary conserved target, SOCS3. This protein is involved in inflammatory responses and keratinocyte proliferation and differentiation (21). In response to IL-6, which is a cytokine present in the psoriatic lesions, STAT3 transcription factor is activated, which leads to development of psoriatic plaques (30). SOCS3, the target of *miR-203,* functions as an inhibitor of STAT3 activation.

It is suggested that the SOCS3 suppression by *miR-203* in psoriatic lesions would lead to constant activation of STAT3, subsequent infiltration of immune cells, and the development of psoriatic plaques. The *miR-203* function in psoriasis is not mediated through the suppression of one protein, but may instead be the sum of functions of all of its target proteins and their interactions (21).

Overall results in the study by Sonkoly et al. showed that miRNA expression patterns distinguish psoriasis from healthy skin and from atopic eczema skin. Their research outlined a new level of regulatory mechanisms in the pathogenesis of chronic skin inflammation. The psoriasis-specific and disease-specific miRNAs identified might be potential therapeutic targets for chronic inflammatory skin diseases (21).

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE), a systemic disease, and idiopathic thrombocytopenic purpura (ITP), an organ-specific disease, are inflammatory autoimmune diseases affecting the skin and other organs. Because many lupus symptoms also appear in other illnesses, it is sometimes difficult to distinguish SLE from ITP. SLE is characterized by autoantibodies causing damage to skin, joints, kidneys, the central nervous system, and so on. Genetic predispositions and environmental factors are involved in the pathogenesis of SLE. Molecular research on SLE, including DNA, RNA, or protein profiles, has not adequately interpreted the pathogenesis of SLE and the cause of the diversity of symptoms remains unclear. To identify changes in miRNA expression that are specific to each condition, Dai et al. compared the levels of miRNA expression in SLE patients with ITP patients using miRNA micro-arrays. They found 22 SLE- and ITP-related miRNAs, of which 13 miRNAs had the same expression pattern in both SLE and ITP and might be generally associated with autoimmune diseases. For three SLE-related miRNAs, the authors proposed involvement in systemic inflammation, and for another six miRNAs, which were ITP-related, they proposed a function in organ-specific destruction of thrombocytes. Thus, SLE-specific and ITP-specific miRNAs are potential therapeutic targets as potential biomarkers for differential diagnosis of SLE and ITP and are probably involved in the pathogenesis of SLE and ITP (22).

Morphogenesis and maintenance of hair follicles

Because the epidermis and hair follicles are accessible, easy to manipulate genetically, and well characterized (like morphogenesis and stem cell populations), several research groups have chosen the skin as a model system to investigate the functions of miRNA ablation in organogenesis. Mouse epidermis and hair follicles are two closely-related tissues developed from the multipotent surface epithelium in the embryo (23). Thus, several research groups focused on mouse skin morphogenesis to show the involvement of miRNAs in skin differentiation.

miRNA expression analysis

By cloning and characterizing more than 100 miRNAs from epidermis and hair follicles, Yi et al. showed that many skin miRNAs are differentially expressed in the epidermis and hair follicles. Three highly expressed miRNAs in the epidermis were absent in the hair follicles and, conversely, six abundant miRNAs were specific to the hair follicle. The discovered coordinate regulation and differential expression of discrete groups of miRNAs reveal classification of skin miRNAs into discrete families, of which members may be classified on the basis of their predicted targets rather than their genomic location. Therefore, expression of multiple miRNAs with the same target reinforces the developmental program by amplifying the regulation effectors (23, 31). An interesting example is represented by *miR-203*, a skin-specific and psoriasis-specific miRNA that is also induced in the skin during the stratification and differentiation stage. Researchers identified p63, a regulator of stem-cell maintenance in stratified epithelial tissue, as a second conserved target of *miR-203* across vertebrates. *MiR-203* represses the expression of p63 and at least in part acts as a switch between proliferation and differentiation (32).

miRNA ablation

In addition, researchers tested the significance of miRNA function by deleting Dicer in embryonic skin progenitor cells. In the absence of Dicer, mouse epithelium failed to produce mature miRNAs. Epidermal differentiation was largely unaffected in animals lacking the Dicer function, but there was a striking defect in follicle morphogenesis. miRNA deficiency in hair follicle morphogenesis leads to evagination toward the surface of the skin instead of invagination of follicular epithelium progenitors, which proliferate and invade the dermis (23, 33). A similar experiment was carried out by another group, in which they performed epidermal-specific Dicer deletion in the mouse skin. In addition to the observed evagination, hair follicles were stunted, hypoproliferative, and misoriented. In contrast, the epidermis became hyperproliferative. In addition, micro-array analysis of miRNA expression at birth was performed. At this point in time, new hair follicles are still developing and primary hair follicles are beginning to undergo terminal differentiation (34).

Hair growth

Wenguang et al. demonstrated that miRNAs previously associated with hair follicles in the mouse are also

expressed in the adult skin of goats and sheep. To identify mammalian miRNAs that might function in hair growth, they performed an expression analysis of 159 miRNAs in adult body skin from goats and sheep. Their results using micro-array analysis imply that miRNAs have function in mammalian hair follicle growth and development (35).

In summary, loss of epithelial Dicer, and consequently miRNAs, produces several distinct defects in the skin, such as failure of dermal papilla and hair-follicle maintenance, and epidermal evagination of clusters of cells. Therefore, Dicer and its miRNA targets may be critical for regulating the interactions essential for skin and epithelial appendage morphogenesis (23, 34).

Possible applications and further directions

Disease-specific miRNAs identified in psoriasis-affected skin and atopic eczema skin may be useful as potential therapeutic targets in suppression of chronic skin inflammation. In addition to potential therapeutic approach, miRNAs could be also useful as diagnostic biomarkers (as in cases of SLE- and ITP-related miRNAs). If tested positive, disease-specific miRNAs in skin may represent novel diagnostic and therapeutic strategies for the treatment of skin diseases.

Abbreviations

Ago = argonaute protein
dsRNA = double-stranded RNA
IRAK1 = interleukin-1 receptor-associated kinase 1
ITP = idiopathic thrombocytopenic purpura
miRNA = microRNA
mRNA = messenger RNA
nt = nucleotide
Pol II, Pol III = polymerase II, polymerase III
RNAi = RNA interference
3' UTR = 3' untranslated region
siRNA = small interfering RNA
SLE = systemic lupus erythematosus
SOCS3 = suppressor of cytokine signaling 3
STAT3 = signal transducer and activator of transcription 3
RISC = RNA-induced silencing complex
TGF-β = tumor growth factor-beta
TNF-alpha = tumor necrosis factor-alpha
TRAF6 = tumor necrosis factor (TNF)-receptor-associated factor 6

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