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MicroRNA in skin diseases

MicroRNAs are essential regulators of various cellular processes such as cell growth, differentiation, apoptosis, and the immune response, acting as factors for translational repression and/or degradation of target messenger RNA. Currently, microRNAs are considered as promising biomarkers and therapeutic targets for different pathological conditions. Skin may serve as a convenient model for microRNA modulation studies due to the comparatively easy access to targets cells. Cutaneous diseases are characterized by multiple intercellular communication pathways, triggered by diverse stimuli and mediated by heterogenous regulators, including microRNAs. The goal of this article is to summarize the state of research in dermatology concerning the action of microRNAs as epigenetic modulators.

Key words: atopic dermatitis, lichen planus, microRNA, psoriasis, skin disease, vitiligo

MicroRNAs belong to a class of small non-coding RNAs that regulate various cell functions via binding to target mRNAs, resulting in mRNA degradation and inhibition of translation [1]. MicroRNAs bind to and cleave messenger RNAs of target genes or inhibit protein translation [2]. To briefly describe the genesis of microRNAs, it is accepted that synthesis starts in the nucleus where the primary transcript, pri-microRNA, is synthesized. These transcripts are then cleaved by RNase III-type nuclease, leading to the formation of hairpin structures; pre-microRNA of 60-70 nucleotides. These structures interact with protein exportin and are translocated to the cytoplasm. The enzyme Dicer forms an asymmetric microRNA duplex which contacts with RNA-induced silencing complex (RISC), with one part of the duplex becoming a mature microRNA thereafter.

Novel approaches to target microRNAs have recently emerged allowing modulation of microRNAs levels in diverse pathological processes [3], thus making them promising targets for molecular-based diagnostics and therapy. MicroRNA expression patterns are tissue-dependent and relatively stable during various pathological alterations. Cutaneous diseases may serve as an attractive model for *in vivo* studies due to relatively accessible delivery of microRNA modulators to skin lesion sites. Here, we report the present status of research on microRNA expression and functional alterations in skin diseases, in order to more fully understand the role of these molecules in cutaneous pathology.

Psoriasis

Psoriasis is one of the most common skin disorders of multifactorial origin which is characterized by immune-mediated chronic cutaneous inflammation. NF-κB is considered to be a key transcription factor of regulation of psoriatic keratinocyte proliferation. Constitutive activation of NF-κB leads to the enhanced expression of proinflammatory cytokines, chemokines, and growth factors that facilitates immune cell trafficking into the skin, leading to keratinocyte hyperproliferation [4]. As a result of NF-κB activation, there is also an increase in miR-31, observed in lesional and non-lesional skin of psoriatic patients. Up-regulated miR-31 diminishes the expression of protein phosphatase 6 which is a component of the cell cycle regulation system, followed by an increased number of cells in S phase of the cell cycle. MiR-31 up-regulation in psoriatic skin is also induced by transforming growth factor-β and results in endothelial cell activation and leukocyte migration into the skin. In turn, miR-31 down-regulation in psoriatic keratinocytes via serine/threonine kinase 40 causes NF-κB signalling inhibition and suppression of inflammatory chemokines CXCL1, CXCL5, CXCL8, and IL1β/IL8 [5]. Up-regulation of miR-31 in keratinocytes accounts for their hyperproliferation and epidermal acanthosis [6, 7]. Remarkably, in normal keratinocytes, miR-31 stimulates differentiation via targeting Notch signalling which is one of the key regulators of epithelial growth/differentiation balance [8].

Besides miR-31, miR-21 is another type of over-expressed microRNA in psoriasis [9]. It is a well-characterized microRNA, the over-expression of which was observed in various cancer types, including melanoma. MiR-21 is a pleotropic regulator of cancer cell biology with a capacity to stimulate cancer cell proliferation, migration, and invasion, as well as inhibition of apoptosis [10, 11]. The latter effect can be seen in psoriatic skin where miR-21 inhibition stimulates apoptosis of T cells, which is estimated to be a promising approach to modulate activated T cells in psoriasis [12]. MiR-21 and miR-125b levels are altered in psoriatic epidermis by ultraviolet B [13]. In mouse epidermal cells, UVB enhances miR-21 expression which results in down-regulation of tumour suppressor programmed cell death protein 4 and is mediated by reactive oxygen species and the MAPK signalling pathway [14]. At the same time,

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miR-21 functions as an angiogenic factor by increasing VEGF levels via ion-selective P2X7 purinergic receptors and modulates the immune response by inducing Th17-biased immunity in psoriatic skin [15]. Therefore, miR-21 acts as a mediator of diverse processes in psoriatic skin, including the immune response, apoptosis, angiogenesis, and UV-induced reactions.

In contrast, microRNA expression profiling by microarray led to the identification of miR-125b as one of the most down-regulated microRNAs, which was confirmed by real-time qPCR analysis. Functional studies revealed that miR-125b facilitates psoriatic keratinocyte differentiation and suppresses keratinocyte proliferation by targeting fibroblast growth factor receptor-2 [16]. In diffuse large B-cell lymphoma, miR-125b modulates the NF-κB pathway which plays a key role in inflammation sustenance in psoriatic skin, as has been mentioned before [17]. MiR-125b negatively regulates tumour necrosis factor α which operates as a crucial cytokine in psoriasis [18]. The functions of microRNAs in psoriasis are outlined in *figure 1*.

In addition to their implication in proliferation, differentiation, and regulation of apoptosis, several microRNAs were found to relate to immunological reactions in psoriatic skin. MiR-138 is involved in maintaining Th1/Th2 balance in psoriatic CD4(+) T cells by targeting transcription factor RUNX3, which is required for T-cell growth and maturation [19]. MiR-210 down-regulation alters transcription factor FOXP3 expression in CD4(+) T cells of psoriatic patients which is responsible for the suppressive capacity of regulatory T cells [20]. For two microRNAs, miR-193b and miR-223, dysregulated expression levels were found both in psoriatic dermal leucocytes and in circulating peripheral blood mononuclear cells [21]. Peripheral blood levels of miR-223 and miR-143 corresponded to specific Psoriasis Area Severity Index scores and showed a decrease after successful treatment with methotrexate for psoriatic lesions [22]. Hence, by interacting with the transcription factors of target genes, microRNAs coordinate both development and activation of immune cells in psoriasis.

Several studies have been performed in search of new blood molecular markers for prognostic purposes. The levels of microRNAs were evaluated before and after adalimumab treatment in lesional skin of Aldara-induced psoriasis-like skin inflammation, but cytokine expression levels after adalimumab treatment did not correlate with microRNA levels, some of which remained dysregulated for more than 80 days after treatment [23]. Another study revealed that anti-tumour necrosis factor α therapy affects microRNA serum levels, but no correlation with disease severity was found [24]. The levels of microRNAs are thus dysregulated in blood of psoriatic patients, and some of the altered molecules could serve as a marker to monitor efficacy of treatment for psoriasis after their objective evaluation.

Atopic dermatitis

In the field of immunopathology, miR-155 is related to a well-characterized microRNA type; its expression inversely correlates with Th17 levels in patients with acute myocardial infarction [25], miR-155 regulates IL-6 and IL-8 levels in intestinal myofibroblasts [26], and miR-155-deficient mice demonstrated abnormal CD8(+) T-cell-mediated immune response to viral antigens [27].

Pivarcsi *et al*. reported that in atopic dermatitis, miR-155 is produced primarily by CD4(+) T cells and dendritic cells (*figure 2*). MiR-155 up-regulation sustains chronic skin inflammation by modulating CD4(+) T-cell activity and direct targeting of CTLA-4 protein, which functions as a negative regulator of T-cell activation [28, 29]. MiR-155 null mice demonstrated decreased levels of IL-2 and IFN-γ and presented fewer class-switched antibodies after immunization [30]. MiR-155 inhibition decreased the number of Th17 cells and the levels of IL-17 and its mRNA, whereas miR-155 over-expression induced the elevation of Th17 cells, as well as IL-17 expression, in transfected atopic dermatitis CD4(+) T cells. Moreover, in atopic dermatitis skin, a negative correlation was observed between miR-155 expression and suppressor of cytokine signalling-1 (SOCS-1), which stimulates IL-2, IL-3, IL-6, and IFN-γ expression via JAK-STAT transcription factors [31]. Thus, miR-155 contributes to the development of atopic dermatitis via the regulation of differentiation and functioning of CD4(+) T cells.

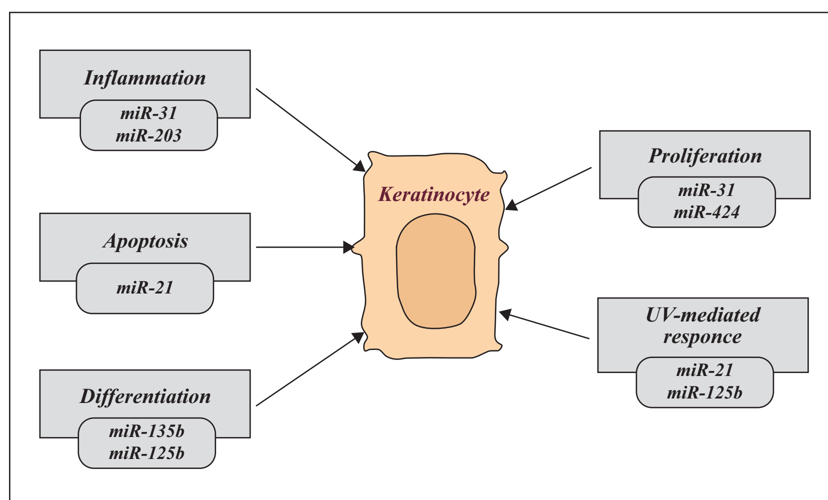

Figure 1. Psoriasis-associated microRNAs.

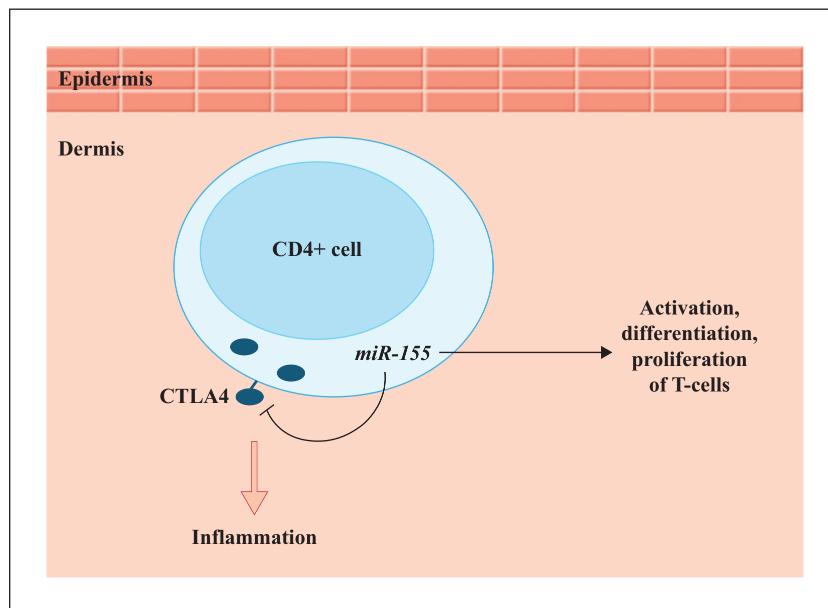

Figure 2. Implication of miR-155 in atopic dermatitis: miR-155 acts as a negative regulator of cytotoxic T lymphocyte-associated antigen 4 (CTLA4), thereby increasing inflammation in affected skin. Moreover, over-expression of miR-155 in dermal cells results in activation, proliferation, and differentiation of CD4(+) T cells.

As well as miR-155, the study of Akdis *et al*. showed that miR-146a plays a role in immune-mediated inflammation and acts as a negative modulator of chemokine CCL5 and CCL8 expression via targeting of the NF-kB signalling pathway. The over-expression of miR-146a was revealed in atopic dermatitis skin. MiR-146-deficient mice exhibited inflammation in the skin, which was characterized by elevated levels of IFN-γ, CCL5, CCL8, and ubiquitin D [32]. The keratinocyte proliferation/differentiation balance is altered in atopic dermatitis skin and controlled by miR-31, similar to psoriasis, by mediating the Notch signal pathway, the suppression of which results in impaired epidermal cell differentiation [8].

For a better understanding of the correlations between lesional skin and systemic response, serum levels of microRNAs were studied. A comparative assay of microRNA profiling in atopic dermatitis demonstrated elevated serum levels of miR-203 in children, which was different to that in adult atopic dermatitis patients. MiR-203 up-regulation in serum corresponded to higher serum levels of IgE. Moreover, miR-483-5p levels were elevated in serum of children with atopic dermatitis. Previous studies revealed elevated miR-483-5p levels in sepsis. Therefore, miR-483-5p dysregulation may be due to a non-specific response to inflammation and should be further elucidated. Additionally, this study showed that microRNA levels are altered in the urine of atopic dermatitis patients, although the exact origin of this remains unclear and requires further investigation [33].

Allergic contact dermatitis

MiR-21, miR-142-3p, miR-142-5p, and miR-223 were found to be up-regulated in human skin sensitized by diphenylcyclopropenone. Similar alterations were revealed in a mouse model of contact dermatitis [34]. As has been previously reported, miR-21 is one of the best characterized microRNA types implicated in carcinogenesis, immune response, and cell injury. The capabilities to modulate inflammatory reactions may be attributed to its impact on NF-κB functioning, as well as transforming growth factor-β signalling [35]. The other microRNAs mentioned are also implicated in immune reactions. MiR-223 drives macrophage polarization [36], miR-142-5p regulates the function of macrophages and their ability to activate fibroblasts [37], and miR-142-3p expression is associated with innate immunity reactions [38]. Summarizing the results for microRNAs regarding allergic contact dermatitis, these data are in line with the established view on allergic contact dermatitis as a type of immunopathology characterized by a delayed hypersensitivity reaction, such that microRNAs trigger signal pathways to activate immune cells [39].

Lichen planus

Most of the studies on microRNAs in lichen planus are concerned with oral forms of the disease which are considered potentially malignant. A genome-wide microRNA study on oral lichen planus patients identified 16 differentially expressed microRNAs, as compared to healthy controls. Most of the mRNAs under regulatory control of the above-mentioned microRNAs corresponded to proteins which are involved in cell proliferation, apoptosis, ion transport, and regulation of immune processes [40]. Salivary samples from patients with oral squamous cell carcinoma and lichen planus were also studied for microRNA-specific patterns and miR-27b was shown to be the only microRNA type which differed between oral squamous cell carcinoma, lichen planus, and healthy controls [41]. Another study identified a negative correlation between the levels of miR-27b and miR-125a and disease severity [42, 43]. The

Table 1. Differentially expressed microRNAs in skin diseases discussed in this review.

Skin disease	MicroRNA	Regulation	References
Psoriasis	miR-21	Up	[12, 13]
	miR-31	Up	[5, 6]
	miR-125b	Down	[13, 16]
Atopic dermatitis	miR-146a	Up	[32]
	miR-155	Up	[28]
	miR-203	Up	[33]
	miR-483-5p	Up	
Allergic contact dermatitis	miR-21	Up	[34]
	miR-142-3p	Up	
	miR-142-5p	Up	
	miR-223	Up	
Hailey-Hailey disease	miR-125b	Up	[59]
Localized scleroderma	miR-92a	Up	[53]
	miR-196a	Down	[52]
	let-7a	Down	[55]
Neurofibromatosis type 1	miR-486-3p	Down	[65]
Vitiligo	miR-25	Up	[68]
	miR-146a	Up	[67]
	miR-191	Up	
Cutaneous T-cell lymphoma	miR-150	Down	[80]
	miR-223	Down	[78]
Squamous cell carcinoma	miR-125b	Down	[81]
	miR-193/365-1 cluster	Down	[83]
Basal cell carcinoma	miR-183	Increased in nodular relative to infiltrative types of basal cell carcinoma	[84]
Merkel cell carcinoma	miR-203	Down	[90]
Melanoma	miR-17	Up	[101]
	miR-18b	Down	[102]
	miR-29c	Decreased in metastatic tumours compared to primary melanoma	[104]

microRNA profile of salivary exosomes was studied by Lee *et al.* in patients with oral lichen planus to identify possible disease-related molecules. In this report, miR-4484 was the most up-regulated microRNA type [44]. This finding supports other research in which miR-4484 is proposed to be a potent biomarker for early-stage cervical squamous cell carcinoma, although its precise pro-carcinogenic role at the present time is unclear [45].

Aberrant promoter methylation of the miR-137 gene was found in lesional epithelium in 35% of patients with oral lichen planus and in 58.3% of oral squamous cell carcinoma patients, but not in healthy controls. This methylation may be an early epigenetic alteration in oral cancer and precancerous lesions, as DNA methylation abnormalities are often reported to accompany neoplastic transformation [46].

MicroRNAs that are known for their pro-/anti-carcinogenic properties and found to be dysregulated in oral lichen planus are summarized in *table 1*.

MiR-26b was found to be down-regulated in oral lichen planus lesions compared to healthy controls and miR-29a was dysregulated in oral lichen planus compared to squamous cell carcinoma [47]. MiR-26b down-regulation leads to an increase in the inflammation mediator, cyclooxygenase-2 [48]. On the other hand, miR-26b and 29a showed features of tumour suppressors by inhibiting cancer cell migration and invasion [49]. This corresponds to an inflammatory origin of lichen planus which is considered as a chronic premalignant disorder. In oral lichen planus lesions, the levels of miR-146a and miR-155 were increased [50]. Another study revealed miR-155 elevated levels in oral lichen and lichen sclerosus [51]. Again, these results are sustained by various immunoregulatory capacities, such as the effect of miR-146a and miR-155 on CD4(+) T-cell differentiation into Th1/Th2 subtypes. Further studies are needed to elucidate the role of microRNAs in cutaneous lesions of lichen planus. It is essential to establish the interaction between specific microRNA profiles and aetiological agents of lichen planus which could be of diagnostic importance in the future.

Localized scleroderma

MicroRNA studies of scleroderma are mostly concentrated on their role in basic aberrations of the disease. Ihn *et al.* identified decreased miR-196a levels in lesional skin and serum of localized scleroderma patients. Further application of miR-196a specific inhibitor in cultured dermal fibroblasts led to up-regulation of collagen type 1, the excess accumulation of which causes fibrosis [52]. The same group provided evidence that TGF-β activation triggered by miR-92a up-regulation in skin of scleroderma patients may also

result in excessive collagen expression and accumulation [53].
miR-7 under-expression was observed in skin and serum in patients with localized scleroderma. MiR-7 inhibitor transfection in normal fibroblasts stimulated α2(I) collagen formation, followed by abundant deposition of collagen type I [54]. MiR-let-7a was found to be down-regulated in systemic and localized scleroderma. Injections of let-7a entailed the increase of α1(I) and α2(II) collagen expression. The injection of let-7a into mice skin induced the decrease of dermal thickness and collagen deposition [55]. At the present time, there is no data on microRNA profiling of lesional skin in localized scleroderma, but hierarchical clustering analysis that followed the profiling of skin samples in systemic scleroderma patients revealed that 18 of 26 altered microRNAs belonged to only one microRNA cluster, localized on chromosome 14q32.3 [56]. At present, microRNA study of localized scleroderma is mostly concentrated on abnormalities of collagen synthesis in scleroderma, while further widening of the scope of research would help to elucidate precise mechanisms of such alterations.

Bullous diseases

Hailey-Hailey disease is an autosomal dominant disorder characterized by the formation of superficial blisters in the epidermis which are often transformed into erosive lesions. The disease is caused by intracellular calcium imbalance because of the mutations in the *ATP2C1* gene which encodes Ca^{2+}/Mn^{2+} ATPase protein 1. Acantholysis is the most significant histological feature of the disease which is caused by a desmosomal defect [57]. The transcription factor Nrf2 is considered to be one of the regulators of such a defect, as its activation results in structural alterations of desmosomes by targeting miR-29a/b [58]. Tight junctions, which are normally responsible for epidermal barrier functioning and transepidermal water loss, are also impaired in Hailey-Hailey disease, as Talora *et al*. showed in their study in which oxidative stress induced miR-125b over-expression in lesional skin-derived keratinocytes, leading to suppression of Notch1 and p63 signalling and deregulation of tight junctions [59].

Hair loss

MicroRNA profile alterations were registered in dermal papilla cells after treatment with 5α-dehydrotestosterone, and more than 60 microRNAs were found to be dysregulated. Altered microRNAs are involved in cell growth, cell cycle, apoptosis, senescence, and oxidative stress induction which is relevant to the effects of 5α-dehydrotestosterone in dermal cells [60]. Daloii *et al.* identified miR-221, miR-125b, miR-106a, and miR-410 as the most up-regulated in dermal cells of androgenic alopecia patients [61]. miR-125b is known to act as a repressor of stem cell differentiation [62], miR-221 is implicated in vascular remodelling [63], and miR-410 up-regulation suppresses vascular endothelial growth factor expression A [64], although the precise role of these molecules in the development of alopecia needs to be clarified. Taken together, these data implicate microRNA in the control of hair follicle development and functioning via growth factors.

Neurofibromatosis

Based on microarray analysis followed by applied hierarchical clustering, differential microRNA patterns in malignant peripheral nerve sheath tumours and dermal neurofibromas in neurofibromatosis type I were identified. MiR-486-3p, one of the most under-expressed microRNAs in dermal neurofibromas, targets PTEN, a component of the RAS-PI3K-AKT signalling pathway, a regulator of cell proliferation, differentiation, and survival. MicroRNAs which were altered in malignant peripheral nerve sheath tumours participated in the regulation of cellular processes generally accepted as oncogenic events; cell adhesion abnormalities, epithelial-mesenchymal transition, cell cycle progression, and aberrant RAS-MAPK signalling [65]. Moreover, Bao *et al.* showed that serum levels of miR-24 may be used to differentiate between sporadic malignant peripheral nerve sheath tumours and neurofibromatosis type I malignant peripheral nerve sheath tumours, which may help the diagnosis of neurofibromatosis type I [66].

Vitiligo

The expression levels of 20 microRNAs differed between vitiligo transgenic Rag1KO mice and control group animals. Two of them, miR-146a and miR-191, were up-regulated in serum of vitiligo mice and non-segmented vitiligo patients. The authors proposed the relevance of deregulated microRNAs as possible vitiligo markers and potential therapeutic targets [67]. As mentioned above, miR-146a is over-expressed in atopic dermatitis and regulates the differentiation of immune cells which may be the consequence of oxidative stress-mediated immune response in vitiligo. MiR-25 levels were elevated in blood and lesional skin in vitiligo patients. This study identified that oxidative stress induced miR-25 over-expression by demethylation of the promoter region of miR-25. On the other hand, MITF-miR-25 interaction was established to promote H_2O_2-induced melanocyte damage and dysfunction. MiR-25 inhibits the synthesis and release of stem cell factor and basic fibroblast growth factor by keratinocytes. This has a protective impact on melanocyte survival, directly influencing proliferation and differentiation of melanocytes [68, 69]. Another expression study revealed that the levels of miR-224-3p and miR-4712-3p were elevated and those of miR-39-40-5p were down-regulated in peripheral blood mononuclear cells of vitiligo patients. Differentially expressed microRNAs were associated with immune system dysfunction [70].
Individuals with TT and TC polymorphisms in the miR-196a-2 gene, combined with elevated levels of tyrosinase, have an increased risk of developing vitiligo, as compared to those with CC genotype and normal tyrosinase levels [71]. The CC genotype of miR-196a-2 rs11614913 is associated with a decreased expression of tyrosinase-1 and correlates

with the lowered levels of reactive oxygen species. Thus, the C allele of miR-196a-2 protects against oxidative stress-mediated cell damage of melanocytes and diminishes the risk of developing vitiligo [72].

Skin cancer

Cancer is one of the pathologies in which the role of microRNAs was first established. The initial observation concerning microRNA dysregulation in cancer was made soon after microRNA pioneering studies were reported [73]. The results of numerous investigations on microRNA in skin cancer are presented in detail in several reviews. Therefore, we will briefly describe the present state of microRNA research in skin malignancies.

Cutaneous lymphoma

Microarray profiling confirmed by qRT-PCR identified that aberrant miR-203, miR-205, and miR-326 expression may serve to differentiate between cutaneous T-cell lymphoma and inflammatory skin diseases including psoriasis, atopic dermatitis, and contact dermatitis [74]. The early stages of mycosis fungoides are characterized by a microRNA expression pattern distinct from that associated with atopic dermatitis, however, these two pathologies may have similar clinical features [75]. Again, cutaneous anaplastic large cell lymphoma has a microRNA profile different from that of inflammatory skin disorders [76]. The 30% of aberrantly expressed microRNAs had abnormal promoter methylation status in their respective genes in mycosis fungoides and CD30+ primary cutaneous anaplastic large cell lymphoma [77]. A functional study on one of the most down-regulated microRNAs, miR-223, was carried out in cutaneous T-cell lymphoma cell lines that was associated with a reduction in tumour cell growth and colony formation. MiR-223 directly targets the transcription factors E2F1, MEF2C, and TOX which are necessary for CD4+ cell maturation [78]. Moreover, miR-223 levels differed between peripheral blood of Sézary syndrome patients and healthy controls in up to 90% cases [79].

The inoculation of immunodeficient mice with lymphoma cells transfected with miR-150 was shown to promote survival. Furthermore, miR-150 was shown to be capable of suppressing invasion and metastasis *in vivo* by targeting the chemokine receptor of CD4+ T cells in cutaneous T-cell lymphoma [80].

Squamous cell carcinoma

MicroRNAs of let-7 and -125 families are down-regulated in squamous cell carcinoma. MiR-125b may control growth, migration, and invasion of squamous cell carcinoma cells by directly targeting the matrix metalloproteinase-13 gene [81]. The MiR-let-7 microRNA cluster is an oncosuppressive microRNA which is dysregulated in various cancer types [82].

In squamous cell carcinoma, microRNA profiles were evaluated in skin primary tumours and in tumours formed after induction by phorbol 12-myristate 13-acetate and 7,12-dimethylbenz[a]anthracene *in vivo* and compared with cutaneous papillomas. Most of the deregulated microRNAs were identified in the papilloma stage. The miR-193/365-1 cluster was down-regulated in squamous cell carcinomas and papillomas. Further studies *in vitro* showed the capability of these microRNAs to block cells in G1 phase of the cell cycle. Functional studies *in vivo* confirmed that miR-193b/365-1 acts as a tumour suppressor. The level of expression was shown to be greater in squamous cell carcinoma cells with epithelial cell characteristics relative to tumour cells of mesenchymal type [83].

Basal cell carcinoma

High-throughput sequencing for microRNA expression profiles in basal cell carcinoma has made it possible to differentiate between nodular and infiltrative types of tumour. MiR-183 expression was shown to differ between the two above-mentioned histology types of basal cell carcinoma. Based on a search for predicted targets, miR-183 was shown to directly regulate genes involved in morphogenesis, differentiation, and apoptosis [84].

Kaposi's sarcoma

The 25 microRNAs identified in Kaposi's sarcoma-associated herpesvirus (KSHV) are involved in virus life cycle regulation. Virus replication consists of latent and lytic phases. The lytic state is necessary for viral spread, while the latent phase is essential for induction of carcinogenesis. The KSHV microRNA, miRK9(*), targets mRNA encoding the major lytic switch protein which regulates virus reactivation [85]. KSHV-encoded microRNAs control multiple pathways that are crucial for stability of latent infection, including regulation of histone modification [86]. Deletion of a microRNA cluster in the KSHV genome, consisting of 14 miRNAs, led to an activation of lytic replication by suppressing the NF-κB signal pathway. This confirms the impact of virus microRNAs and a host signal network of interactions on KSHV survival [87].

Merkel cell carcinoma

Eight differentially expressed microRNAs were identified in Merkel cell carcinoma (MCC) tissues relative to melanoma, squamous cell carcinoma, basal cell carcinoma, and normal skin. The same microRNAs and miR-340 were dysregulated in a Merkel cell carcinoma cell line [88]. Merkel cell polyomavirus (MCV)-positive tumours showed elevated levels of miR-34a, miR-30a, miR-142-3p, and miR-1539, as compared to Merkel cell polyomavirus negative-tumours, however, the authors did not find differences between progressive and metastatic stages of the tumour [89]. Another study on differential expression patterns of MCV- and MCV+ MCC revealed six microRNAs, of which miR-30a-3p, miR-30a-5p, miR-375, miR-34a, and miR-769-5p were up-regulated, and miR-203 down-regulated. Further investigation of miR-203 during the development of MCC revealed that miR-203 can affect cell cycle dynamics, by increasing the number of cells in G1 phase and diminishing the number of cells in G2 phase. It should also be noted that miR-203 targets the protein survivin (a negative regulator of apoptosis) in MCV- MCC cells [90].

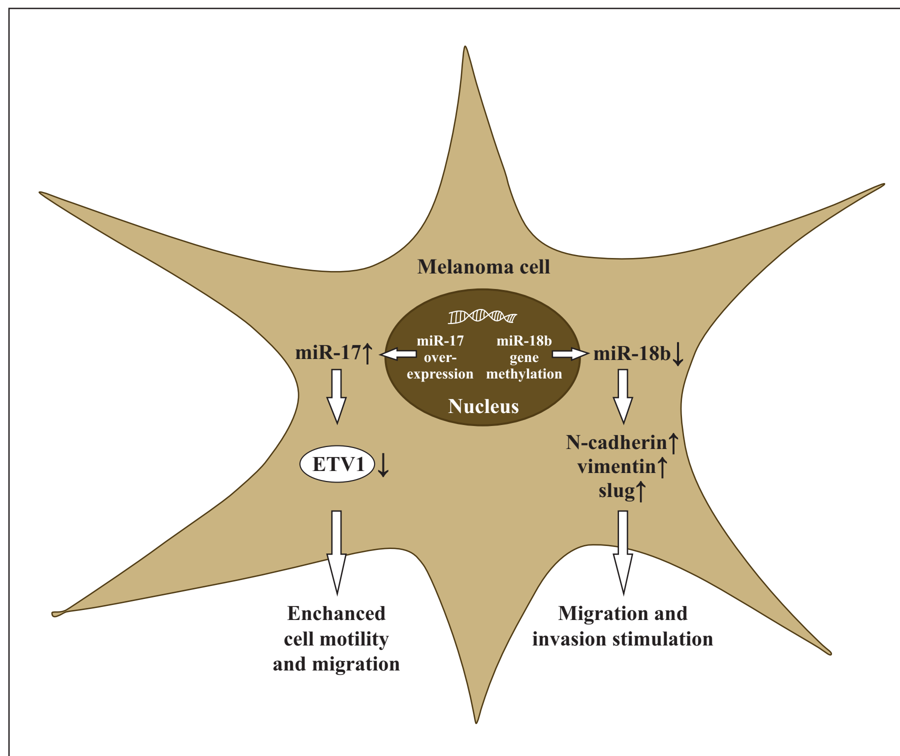

Figure 3. Regulation of melanoma progression by miR-17 and miR-18b. Up-regulation of miR-17 inhibits expression of ETS variant 1 protein (ETV1), which affects melanoma cell motility and migration. MiR-18b under-expression, caused by methylation of the gene, activates migratory and invasive features of melanoma cells.

Melanoma

Since the first comparative study on melanoma cell microRNA expression, reported in 2006 [91], numerous papers were published on differences in microRNA profiling of melanoma versus benign melanocytic tumours, microRNA alterations in peripheral blood [92-95], as well as attempts to reveal microRNA markers of poor prognosis and survival [96-98]. The differences in microRNA levels depend on the *BRAF* status of melanoma [99]. MicroRNA types vary according to mutational status; miR-565 levels were higher in *BRAF*-negative melanomas and miR-663 levels were lower in *NRAS*-positive tumours, compared with *BRAF/NRAS* wild-type cases [96].

At the same time, the analysis of blood samples from more than 50 melanoma patients and 30 healthy volunteers revealed significant alterations in microRNA levels only in advanced disseminated melanomas, as compared to controls. This observation points to the absence of an adequate serum microRNA marker for early diagnosis of melanoma at the present time [100].

The most recent studies in melanoma cell biology have revealed that oncogenic miR-17 regulates melanoma cell motility via translational repression of transcription factor ETV1, which acts as a tumour suppressor and may be implemented in melanocyte malignant transformation [101]. MiR-18b is down-regulated in melanoma cells and melanoma clinical specimens, as compared to melanocytic nevi. MiR-18b targets protein MDM2, which is important for cell cycle control, and regulates proapoptotic p53. Stable over-expression of miR-18b results in an increase in apoptosis of melanoma cells, as well as suppression of cell proliferation and colony formation. Moreover, miR-18b down-regulation stimulates migratory and invasive capacities of melanoma cells via N-cadherin, slug, and vimentin over-expression (*figure 3*) [102].

Several studies have analysed melanoma pathology and microRNA expression levels. Oord *et al*. correlated miR-200a and miR-200c levels with melanoma thickness. The loss of miR-200c expression was observed in invasive (front) margins of melanoma which the authors related to a microRNA role in tumour progression and metastatic development [103]. MiR-29 levels were associated with advanced American Joint Committee on Cancer (AJCC) melanoma stages, but correlated with overall survival in melanoma AJCC Stage III [104].

Conclusion

Despite the fact that almost two decades have passed since the initial discovery of microRNAs, the evident impact of these molecules on the regulation of biological processes in living systems is highly significant, as supported by the growing number of reports on their function in healthy and pathological states. The data on microRNA support their usefulness as biomarkers for disease and monitoring of treatment efficacy. MicroRNAs are implicated in cell growth, differentiation, and apoptosis in skin, through targeting signalling systems and expression of effector pathways which are crucial for skin homeostatic maintenance. MicroRNAs are essential components of immune-mediated

reactions which are present in most cutaneous disorders. Today, there is no conclusive evidence of a correlation between serum and tissue microRNA levels in inflammatory or cancer cutaneous diseases, and such data could serve as a promising basis for optimization of treatment and diagnosis, and therefore, this issue requires further investigation. Some recent results on the molecular pathogenesis of skin disorders favour the notion that microRNAs are also implicated in cell injury and intercellular communication. Modulation of microRNAs may affect the intensity of these processes which may be of translational relevance. ■

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