Importance of microRNAs in Skin Oncogenesis and Their Suitability as Agents and Targets for Topical Therapy

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Keywords

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Abstract

Skin cancer is the most common cancer worldwide, with rapidly increasing incidence and consistent mortality. Skin cancer encompasses melanoma and non-melanoma skin cancer, which in turn is mainly divided into cutaneous squamous cell carcinoma and basal cell carcinoma. Small noncoding microRNAs (miRNAs) regulate protein expression after transcription and play a role in the development and progression of skin cancer. Deregulated expression of miRNAs in skin cancer is associated with cell proliferation, angiogenesis, metastasis, apoptosis, immune response, and drug resistance. Specific patterns of miRNAs in specific skin cancer types can be used as diagnostic markers. For therapeutic purposes, both miRNA and chemically modified variants thereof as well as miRNA antagonists (antagomiRs) or RNA inhibitors may be applied topically. Due to their specific physicochemical properties, physical or chemical diffusion promoters are used with varying degrees of success. There is no question by now that such preparations have a high potential for the treatment of epithelial skin tumors in particular.

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Introduction

MicroRNAs (miRNAs) are noncoding RNAs, which post-transcriptionally regulate protein expression by binding to the 3' untranslated region (3'UTR) of target mRNAs. Thereby, miRNAs induce translational repression or mRNA cleavage. The individual miRNA variants are subject to very different, mostly, tissue-specific expression and regulation patterns, which play a key role in a large number of physiological and pathophysiological processes. The miRNAs described so far have been named and catalogued in a public database (miRBase) in accordance with standardized criteria, with more than 12,000 variants now recorded [1–7]. miRNAs interact with transcription factors in a regulatory network and control basal cell biological processes (Fig. 1). The pattern and quantity of the miRNAs expressed in the cell nucleus are tissue-specific and allow conclusions to be drawn about the functional state of the cell, such as its division and differentiation status. Although initial data are available on miRNA patterns in skin tissue and specific skin diseases, there is a need to characterize new miRNA pathways. Since the integration of miRNAs into regulatory processes is also of vital importance in transformation processes of the cell (e.g., in oncogenesis), there is already an intensive discussion about the possibility of using miRNAs as

Fig. 1. Overview of the role of miRNAs in the regulation of physiological and pathophysiological processes in cells.

therapeutic target structures. Tumor-specific patterns of deregulated miRNAs in frequent skin tumors have been identified, which may allow a targeted therapeutic approach [8]. This could be achieved by intracellularly targeting and substituting certain miRNAs (so-called miRNA mimetics), but also by the use of synthesized oligonucleotides as antagonists of special overexpressed miRNAs (so-called antagomiRs) or target protectors to block selective miRNA-binding sites (RNA inhibitor [RNAi]) [8]. For the development and establishment of miRNA-based therapies, potential off-target effects as well as questions of chemical stability, release, distribution, and immune stimulation have to be considered and ensured or excluded. In addition, it is known that some tissues are able to partially absorb miRNAs via endocytosis [9]. The susceptibility of miRNAs to proteases may also be relevant for their chemical stability [10]. It is also known about cells with accelerated division behavior (e.g., tumor cells) that transiently released miRNAs are as well eliminated faster, making them less suitable as therapeutic target structures [11]. Various experimental

approaches have been described regarding the use of miRNA-based therapies for the treatment of skin tumors, but there have been only a few clinical investigations so far [12, 13].

miRNA Biogenesis and Function

miRNAs are endogenously expressed small noncoding RNAs (20–22 nucleotides) that occur both intra- and intergenically [14]. Besides miRNAs, noncoding RNAs also include small-interfering RNAs (siRNAs), piwi-interacting RNAs, small nuclear RNAs, and small nucleolar RNAs [15, 16]. The primary miRNAs are transcribed by RNA polymerase II (Fig. 2) [17]. The resulting long (~1 kb) transcript forms a hairpin loop, which is nuclear-cleaved by the Drosha RNase III endonuclease in a 60–70 nt precursor miRNA (pre-miRNA) [18]. Ran-GTP and the export receptor exportin-5 actively transport the pre-miRNA from the nucleus to the cytoplasm. Here, the pre-miRNA is further processed by the RNase III endonucle-

Fig. 2. Overview of the steps of biosynthesis of miRNA, their regulation, and functional integration.

ase Dicer, which cleaves the hairpin loop, resulting in an miRNA:miRNA duplex. One strand of the miRNA:miRNA duplex, the mature miRNA, is loaded into the RNA-induced silencing complex (RISC), while the other strand is degraded [18]. By complementarity of 2–8 residues of the miRNA, the RISC is guided to an miRNA seed sequence in the 3'UTR of target mRNAs [19]. The binding of the miRNA-RISC complex induces a translational

repression or destabilization of mRNA [20, 21]. Because miRNAs do not need a perfect complementarity to the targeted 3'UTR, 1 miRNA has the potential to regulate the expression of hundreds of genes [10, 22]. miRNAs were shown to have regulatory functions in a variety of processes such as embryonic development [23], metabolism [24], cell proliferation [25], as well as disease development and progression [26].

miRNAs in Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common invasive skin cancer in the world. It arises from the basal skin cell layer dividing the epidermis from the dermis. BCC development is mainly induced by UV radiation [27]. The constitutive activation of the hedgehog signaling pathway, induced by inactivating PTCH1 mutations, represents the most frequent oncogenic transformation in BCC [28–30]. Metastasis of BCC is unusual; however, metastasized disease has a poor prognosis [31]. The first study on miRNAs in BCC compared the expression pattern between nodular and infiltrating disease. In their analyses, Heffelfinger et al. [32] identified 20 miRNAs with significant differences in expression between nodular and infiltrative BCCs. Furthermore, they validated let-7g and miR-183 with an increased expression in nodular BCCs, while miR-150, miR-31, miR-146a, and miR-886-5p had a significant higher expression in invasive BCCs [32]. In a microarray-based analysis, miRNA expression was investigated in BCC lesions and adjacent non-lesional skin [33]. Sand et al. [33] identified 16 significantly upregulated and 10 significantly downregulated miRNAs in BCC lesions. In a second study, Sand and colleagues [34] showed 33 upregulated miRNAs in BCC under neoadjuvant vismodegib therapy by next-generation sequencing. Some studies investigated the functional role of miRNAs in BCC development and progression. miR-203 was shown to be downregulated in BCC lesions in a Hedgehog signaling pathway dependent manner [35]. Overexpression of miR-203 in a BCC mouse model results in the reduction of tumor growth. Additionally, it was shown that the tumor suppressor miR-203 directly targets c-JUN, resulting in a reduced proliferation and delayed G1 to S phase transition [35]. Sun and Jiang [36] demonstrated miR-451a as a BCC tumor suppressor miRNA. In their study, they showed that miR-451a expression is reduced in human and mouse BCCs. Further, they confirmed the transcription factor TBX1 as a direct target of miR-451a. The overexpression of miR-451a suppressed BCC cell growth through G1 cell cycle arrest [36]. The presented studies show that miRNA dysregulation contributes to BCC development and progression. However, the small number of functional miRNA studies in BCCs leads to an intensification of this research for a better understanding of the molecular mechanisms in BCC.

miRNAs in Cutaneous Squamous Cell Carcinoma

The cutaneous squamous cell carcinoma (cSCC) is a skin tumor, derived from epidermal keratinocytes. It is the second most common human cancer with an increasing incidence [37]. The main risk factor for cSCCs is UV radiation, potentiated by immunosuppression [37]. Most patients with primary cSCC have an excellent prognosis. However, metastatic cSCCs are still challenging. Recent studies have analyzed the role of miRNAs in cSCC development, progression, and metastasis. Sand et al. [38] first performed a comparative miRNA analysis between cSCC biopsies and adjacent healthy skin. In their analysis, they showed 13 significantly elevated and 18 downregulated miRNAs in cSCC tumors. miR-31 was shown to be the highest upregulated miRNA in cSCC compared to healthy skin [38]. In functional studies, it was shown that miR-31 overexpression induces cell motility and colony formation ability of tumor cells [39]. In addition, miR-31 was shown to directly target the tumor suppressor RhoTBT1, inducing cell proliferation and invasion in the cSCC cell line A-431 [40]. A well-studied miRNA in cSCC is the oncogenic miR-365. Studies show that miR-365 promotes cSCC proliferation and progression in vivo and in vitro [41–44]. Functional analyses show that miR-365 inhibits apoptosis by directly targeting BAX [44] and forcing the cell cycle progression by NFIB repression [42, 43]. As shown in recent studies, miR-186, miR-221, miR-506, and miR-142-5p contribute to cSCC tumor growth [45–49]. miR-186 promotes proliferation and inhibits apoptosis by targeting RETREG1 [48] and APAF1 [46]. Gong et al. [47] reported that miR-221 promotes cell proliferation and colony growth by repressing PTEN. Furthermore, it was shown that inhibition of miR-506 induces apoptosis and decreases invasion and migration of cSCC cell lines [49]. In this study, LAMC1 and p65 were identified as direct targets of miR-506. Cancer stem cells have the capability of self-renewal, differentiation, and tumorigenesis. Therefore, they are important actors in tumorigenesis and metastasis. miR-142-5p was shown to induce cancer stem cell-like properties in cSCC cells by inhibition of PTEN [45].

Another controversially discussed miRNA in cSCC is miR-199a [50–52]. On the one hand, miR-199a has been shown to inhibit the proliferation and migration of cSCC through targeting CD44 [50]. In addition, Kim and colleagues [51] showed that miR-199a directly regulates the expression of BCAM, FZD6, WNT7a, DDR1, and PODXL, which inhibits migration capability of skin keratinocytes. On the other hand, Wang et al. [52] reported that miR-199a induces the invasion of cSCC cells by sup-

pression of E-cadherin. Other miRNAs are more clearly described as tumor suppressors in cSCC. In a recently published research, miR-497 was reported to target FAM114A2 and SERPINE1 [53, 54], inhibiting cell growth, migration [53], cell cycle progression, as well as cSCC cell viability [54]. miR-34a and miR-181a also interfere with cSCC growth. miR-34a targets HMGB1 and inhibits cancer cell proliferation, migration, and invasion [55]. By directly targeting KRAS, miR-181a mediates MAPK signaling pathway and suppresses cSCC tumor growth in vivo. Cañueto et al. [56] reported that expression pattern of miR-203 and miR-205 may help to predict the prognosis of cSCC. They showed that miR-203 expression is associated with a positive outcome, while miR-205 correlates with a poor outcome of cSCC. Taken together, these studies show that miRNAs play an important role in the establishment, progression, and metastasis of cSCC. miRNAs act both as oncomiRs and as tumor suppressors. Additionally, miRNAs can be used as prognostic markers for the outcome of cSCC patients.

miRNAs in Melanoma

Melanoma is the most lethal form of skin cancer with increasing incidence [57]. miRNA contribution and function in melanoma development, progression, metastasis, and drug resistance have been widely studied [58–62]. For this report, we have focused on prominent melanoma-associated miRNAs and the latest studies of recent years. miR-21 is an established oncomiR that is highly expressed in various cancers. In malignant melanoma, miR-21 has been shown to have significantly increased expression compared to nevi and normal melanocytes [63–65]. Furthermore, plasma miR-21 was reported to be associated with the tumor burden of melanoma patients [66]. Functional analysis showed that miR-21 targets SPRY1, PDCC4, and PTEN; regulates the ERK/NF- κ B signaling pathway; and affects proliferation, migration, and apoptosis [67–69]. In addition, miR-21 increases melanoma invasiveness by targeting MMP3 [70]. The blocking of miR-21 by antisense oligonucleotides improves the sensitivity of the A375 cell line toward cisplatin [71]. miR-211 that is normally enriched in pigmented cells is reported to be downregulated in melanoma cells compared to normal melanocytes [72, 73]. However, miR-211 is regulated by MITF and was shown to regulate cell invasiveness by targeting NUA1 [74], BRN2 [72], and RAB22A [75]. In addition, miR-211 contributes to resistance against BRAF inhibitor [76, 77], while the loss

of miR-211 reduces the sensitivity of melanoma cells to cisplatin [78]. miR-203 was shown to act as tumor suppressor in several cancers [79–83]. Recent research reported a decreased expression of miR-203 in melanoma tissue and a link with prognosis of melanoma patients [84, 85]. Furthermore, low expression of miR-203 has been shown to inhibit migration, invasion, and proliferation of melanoma by targeting BIM1 [86] and SLUG [87]. More recent studies, however, contradict this and show an overexpression of miR-203 as a marker for an early phase of metastasis [88].

miRNAs as Therapeutic Approach

In recent decades, miRNAs have become the focus of attention as novel therapeutic targets. In vivo studies on different mouse disease models have shown the efficacy of miRNA targeting therapeutic strategies [89–93]. Currently, RNA molecules are already being investigated in clinical studies as therapeutic molecules mostly for systemic application. The miR-122 inhibitor miravirsin was tested as a novel therapeutic strategy for HCV infections (ClinicalTrials.gov identifier: NCT01200420) [94, 95]. In addition, patisiran, the first RNAi-based therapy, was approved by the FDA in 2018 [96, 97].

In order to therapeutically influence the intracytoplasmic concentration and function of miRNA (miRNA-based therapy), (1) defective miRNA (or slightly modified miRNA to improve chemical stability) can be substituted or (2) antagomiRs or RNAi can be used to counteract overexpression of miRNA.

One challenge for the therapeutic use of oligonucleotides to replace or inhibit miRNAs is the stability. RNAs are highly fragile for degradation by endo- and exonucleases. Chemical modifications of the oligonucleotide backbone or at the ribose were shown to increase the stability and delivery efficiency for in vivo applications. The substitution of the α -oxygen at the phosphate by a sulfur, methyl, or borano group improves the stability of the oligonucleotides [98]. Introduction of 2'-O-methyl (2'-O-methyl-(2'-O-Me) oligonucleotides) or the incorporation of a 2',4' methylene bridge at the ribose, to form a bicyclic oligonucleotide (locked nucleic acid oligonucleotides), protects against nucleases degradation and improves the binding ability to potential target RNAs [99–101]. The terminal introduction of cholesterol, biotin, or amino modification enhances the cellular uptake and the delivery and can increase the stability of oligonucleotides [101]. For in vivo applications, multiple modifications are

used in combination to achieve the best functional efficiency and stability.

Their respective galenic formulations depend on the physicochemical properties and cannot be fixed in general terms. However, special challenges arise during the development of suitable preparations to ensure the chemical stability of the active substance within a suitable vehicle, to implement sufficient release behavior from the vehicle, to optimize intracellular bioavailability at the target cells, and to observe regulatory, patent, and commercial framework conditions. Although the use of miRNAs as active molecules in topical therapy offers significant advantages over systemic application, it also poses a number of challenges, which will be summarized below. Suitable miRNAs in sufficient and reproducible quality and quantity must be available for the application. The galenic formulation must primarily ensure the chemical and functional stability of the miRNAs, but at the same time, it should also provide a physicochemical framework for the highest possible release and diffusion rate of hydrophilic miRNAs. Depending on the indication for use, cells of the vital epidermis or the upper corium can be regarded as the galenic target compartment within the skin organ. In connection with oncological indications, it is also necessary to realize an optimized distribution behavior of the therapeutic agent intratumorally. When applied to intact epidermis, permeation of the stratum corneum is naturally necessary. Since the epicutaneous application of naked miRNA does not lead to an efficient transfection due to the high hydrophilicity and the large molecular mass, vehicle strategies for transcorneal transport are necessary. The use of preparations on severely barrier-disturbed epidermis, for example, for certain carcinomas, erosive or peracutely inflamed skin, may lead to conditions that make the use of conventional vehicles seem possible. If the stratum corneum is only functionally active to a limited extent, penetration promotion strategies must be considered. For this purpose, physical and chemical methods are available, which offer options for an intact introduction of miRNA, antagomiRs, or RNAis [102].

Physical Methods

The principle of physical penetration promotion is based on the initiation of diffusion through artificial microchannels, which are produced by physical intervention using microneedles, microjets, laser or electroporation, sonophoresis, or iontophoresis for a limited period of time. Various technical procedures and application

strategies have been established and tested for the application of the respective methods. The selection of one of the possible methods depends on the molecular mass of the therapeutic agent and its physicochemical properties and vulnerability. Against this background and for practical reasons, the topical application of miRNAs in intracutaneous tumor tissue is particularly suitable for microneedles or microjets. For this purpose, commercially available systems are already established, so that the prerequisites for the application are largely given and can be adapted to the respective indication [102].

Chemical Methods

The use of chemical penetration promoters or modern vehicle strategies derived from them (so-called supramolecular aggregates) poses a significantly higher challenge. The interaction of such enhancer molecules leads to a targeted interaction with the molecular organizational structure of SC, which leads to changes in the diffusion conditions, especially in the area of the intercellular lipid matrix. Due to the hydrophilic character of miRNAs, enhancers of the polar diffusion route (i.e., alcohols, amides, surfactants, and sulfoxides) are of particular interest. For hydrophilic macromolecules, experience with microemulsion systems, liposome variations, and nanoparticles is available [102]. These colloidal vehicle systems mediate the proportional transfer of the active agent to or into the cell and realize its release in bioactive form. These very complex aggregates are complex to manufacture and very cost-intensive for practical use. The experimental application, especially in animal experiments and diffusion models, clearly shows that the epicutaneous application of miRNAs is possible [103–105]. Furthermore, the use of so-called cell penetrating peptides is propagated [106]. These are peptides that spontaneously permeate cell membranes and can also transport covalently or non-covalently bound nucleic acids or nanoparticles [107]. Data on the siRNA application of so-called “skin penetrating and cell entering” peptides, trans-activating transcription activator peptides, and poly-arginine (poly-R) peptides are available [108–111]. Nanoparticles or aggregates of nanoparticles with spherical nucleic acids have also been investigated in various variations for their suitability [112]. Especially for variations with gold nanoparticles data are available [113]. Variations of liposomal structures have been validated for many years with regard to their suitability as drug delivery systems, also with regard to miRNA [114–119]. Only through the develop-

ment of so-called transfersomes (ultra-deformable liposomes) could incorporated macromolecules such as peptides, DNA vaccines, and proteins be effectively transported transmembrane or transcorneally [120–122]. However, the evidence for the suitability for the effective miRNA transport after epicutaneous application is lacking for transfersomes as well as for further developed variations, such as ethanol-rich ethosomes or transethosomes [16]. In contrast, liposome variants of mixtures of surfactant, ethanol, and cholesterol (secosomes) or of lecithin phospholipids and cationic lipids (LeciPlex) for the transport of siRNA, pre-miRNA, and anti-miRNA have already been successfully investigated [123, 124]. Due to the comparatively uncomplicated production, complexes of miRNA and chitosan were investigated with high expectations [125–128]. Unfortunately, no relevant transfection efficiency was shown, so that their suitability seems questionable. Chemical modifications of miRNA, which increase the stability of the agent and lead to an improved diffusion ability, also attracted attention [129, 130]. Such modifications have also been described for RNAi (self-delivering RNAi) [131, 132].

Conclusions

The therapeutic use of miRNAs, antagomiRs, and RNAis has great potential. The topical application of such biotechnological agents and the realization of a sufficient

bioavailability of bioactive agents in the target cells place the highest demands on galenic development, suitable vehicle, and enhancer strategies as well as the assurance of chemical and biological stability. In addition, special experimental strategies are required to characterize developed preparations preclinically and to produce them in a standardized way. Even though initial data on the effectiveness of topical preparations in animal experiments have not yet been obtained, it is still necessary to develop special experimental strategies.

Conflict of Interest Statement

All authors declare no conflicts of interest.

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Author Contributions

D.G. and J.W. wrote the manuscript. C.S. commented on the manuscript.

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