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Micro RNA profiling in skin care: what have we learned?

Abstract

For a number of years, profiling of the up and down-regulation of specific micro RNAs in response to various skin afflictions has been conducted to expand our understanding of these conditions as well as to find new therapeutic solutions. MicroRNAs represent one of the short non-coding RNA effectors of the RNA interference pathway for post-transcriptional gene silencing. Due to their flexible sequence complementarity requirements for targeting specific messenger RNAs, micro RNAs have the capacity to modulate gene expression of multiple proteins in a cell, thus potentially impacting several signaling pathways. Multiple technologies have been developed to make the study of micro RNA modulation more prolific and mainstream. With the wealth of data that has been accumulated as a result of these expanded analyses, it is worthwhile to inquire about what has been learned and how treatments for skin diseases and disorders have been expanded and improved due to micro RNA profiling.

Keywords: micro RNA, profiling, micro RNA array, skin care, keratinocytes

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Paul Lawrence, Joseph Ceccoli
Director of Bioscience Research and Product Development, Stony Brook University, USA

Correspondence: Paul Lawrence, Director of Bioscience Research and Product Development, 25 Health Sciences Drive, Stony Brook, NY 11790, USA,
Email paul.lawrence@biocogent.com

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Abbreviations: miR or miRNA, micro RNA; siRNA, short-interfering RNA; RNAi, RNA interferencemRNA, messenger RNA

Introduction

The skin represents the largest organ of the human body, and like any other organ is susceptible to a variety of ailments from genetic, pathogenic, and environmental sources.[1,2] Considerable effort has been devoted to ameliorating and eliminating a variety of these conditions, including but not limited to: melanoma, melasma, psoriasis, atopic dermatitis, acne, vitiligo, aberrant skin pigmentation, and ultraviolet (UV) light induced damage. In many cases, a genetic component (or components) has been identified that is either the root cause or contributes to the pathology. One such genetic aspect that has started to receive considerably more attention is the contribution of micro RNAs, one effector arm of the RNA interference pathway.[3–5]

The discovery of RNA interference (RNAi) in the 1990s and the technological applications developed from this biological process rightfully earned its discoverers the Nobel Prize.[3] RNAi modulates gene expression at the post-transcriptional level, where messenger RNAs (mRNAs) of specific genes are sequestered and/or degraded by the short non-coding RNA (ncRNA) effector molecules of this pathway: short interfering RNAs (siRNAs) and micro RNAs (miRNAs or miRs).[3,5] While siRNAs are generally derived from exogenous sources of double-stranded RNA and require exquisite sequence complementarity to anneal to targeted mRNA molecules, micro RNAs are generated endogenously and require only partial sequence complementarity with a target mRNA.[6] The flexible complementarity for annealing to a mRNA allows for greater promiscuity for miRNAs in the selection of targets, thereby one miRNA can affect the expression levels of multiple proteins and impact several signaling pathways within a cell.[7,8]

Research into miRNAs has shown its utility as both a diagnostic tool as well as a therapeutic. In the former case, miRNAs have demonstrated differential expression in response to certain diseases and disorders, much like an innate immune response, and that the miRNAs affected tend to be unique. The benefit from identifying such miRNAs is that they point in the direction of what signaling pathways are active in the wake of certain conditions, thus suggesting potential therapeutic approaches. As a therapeutic, scientists have developed methodologies to enhance the levels of miRNAs that down-modulate harmful signaling pathways (so-called "miRNA replacement therapy") and nullify the post-transcriptional activity of miRNAs that target beneficial gene products through the irreversible binding to synthetic complementary short ncRNAs called "antagomiRs".[9–11] This mini-review will focus on the diagnostic and discovery potential behind current miRNA profiling efforts.

Micro RNA profiling

Since the discovery of how impactful miRNAs can be to gene expression in the cell, researchers started to look to how genetic, pathogenic, and environmental factors could influence miRNAs and differentially regulate their intracellular levels. For example, would infection with a particular virus disrupt the homeostatic levels of particular miRNAs, causing some to be up-regulated and others to be down-regulated? Diagnostic platforms for miRNA expression levels affirmatively answered that outside factors such as viruses can induce changes in the levels of particular miRNAs and that the patterns of miRNA dysregulation are most often unique to the particular form of stress, thus producing specific "miRNA signatures". These "signatures" have been detected *In vitro* in multiple cell lines as well as in several biological specimens such as tissue, serum, throat swabs, and urine.[12–16] In one such instance, there are two different etiological agents for hand-foot-and-mouth disease (HFMD): enterovirus-71 (EV-71) and coxsackievirus A16 (CVA-16). Despite being closely related picornaviruses and producing near identical symptomologies, the differential regulation of miRNAs in response to each viral pathogen is distinctly different, allowing for a way to diagnose which virus is responsible for an infection.[17] Indeed, sometimes the same virus can produce two different types of infection with each producing a unique miRNA response; such is the case with foot-and-mouth disease virus (FMDV) which produced distinct miRNA signatures in serum collected from cattle that were either acutely infected (viremic) or persistently infected (carriers) with FMDV.[12]

Micro RNA profiles of skin conditions

With respect to skin diseases and disorders, significant efforts have been put forth to identify miRNAs that are up and down-regulated in response to different afflictions. Indeed, UV light can induce damage to the keratinocytes of the skin, and a miRNA profiling study determined that the dysregulation of miRNAs is distinct for UV-A and UV-B exposure.[13] As shown in Table 1, UV-A exposure catalyzed in keratinocytes the differential regulation of 27 different miRNAs with 14 down-regulated and 13 up-regulated. With keratinocytes exposed to UV-B, 28 miRNAs were dysregulated with 19 down-regulated and 9 up-regulated, of which only 9 were shared with those detected for UV-A exposure (Table 1). In a similar study, the miRNA signature resulting from UV-A exposure to fibroblasts was evaluated, showing a change in the levels of 12miRNAs with 7 increased and 5 decreased.[18] Notably, only three of the miRNAs detected (miR-30c, miR-181c, and miR-218) in the fibroblast study were shared with those observed in the aforementioned keratinocyte report. All three of these miRNAs have been implicated in the development of cancer, where miR-181c and miR-218 (both down-regulated) have associated roles in tumor suppression and apoptosis,[19,20] while miR-30c (up-regulated) is oncogenic and targets p53.[21] The miRNA response in the skin after exposure to UV radiation was thoroughly reviewed by Syed et al., where they detailed the expanding list of miRNAs whose levels fluctuate subsequent to UV exposure resulting in multiple outcomes.[22]

Certain inflammatory skin conditions have also been profiled for miRNA signatures to assist in diagnosis and treatment, including atopic dermatitis and psoriasis.[14] Psoriasis and atopic dermatitis exhibit similar symptomologies, sometimes clouding diagnosis, thus the determination of the miRNA profiles for each condition could provide the basis for a diagnostic assay to prevent misdiagnosis. Skin tissue exhibiting each skin condition was collected and their relative miRNA patterns of expression profiled against healthy skin, showing a total of 21 dysregulated miRNAs resulting from atopic dermatitis and a total of 29 for psoriasis.[14] Although each distinct form of skin inflammation produced a unique miRNA signature, the two conditions shared 8miRNA fluctuations with corresponding up and down-modulations (Table 1).

Table 1 Differentially regulated miRNAs in response to skin conditions tabulated below are various human miRNAs whose levels are up or down-regulated in response to the indicated skin conditions

UV-A[13]					
↓ miR-10a	↓ miR-130b	↓ miR-376a	↑ miR-96	↑ miR-340	↑ miR-574-3p
↓ miR-18b	↓ miR-210	↓ miR-487b	↑ miR-132	↑miR-376c	↑ miR-886-5p
↓ miR-98	↓ miR-212	↓ miR-494	↑ miR-191	↑ miR-452	
↓ miR-99b	↓ miR-323-3p	↓ miR-598	↑ miR-196b	↑ miR-484	
↓ miR-127-3p	↓ miR-330-3p	↑ miR-23b	↑ miR-224	↑ miR-501-5p	
UV-B[13]					
↓ miR-20b	↓ miR-98	↓ miR-330-3p	↓ miR-503	↑ miR-139-5p	↑ miR-376c
↓ miR-23c	↓ miR-181c	↓ miR-335	↓ miR-532-5p	↑ miR-191	↑ miR-455-3p
↓ miR-29c	↓ miR-218	↓ miR-376a	↓ miR-598	↑ miR-339-3p	↑ miR-501-5p
↓ miR-30c	↓ miR-301a	↓ miR-411	↓ miR-600	↑ miR-361-5p	
↓ miR-96	↓ miR-323-3p	↓ miR-494	↑ let-7c	↑ miR-362-5p	
Atopic dermatitis[14]					
↓ miR-122a	↓ miR-335	↑ miR-17-5p	↑ miR-29a	↑ miR-222	
↓ miR-133a	↓ miR-483	↑ miR-20a	↑ miR-106b		
↓ miR-133b	↓ miR-515-5p	↑ miR-21	↑ miR-146a		
↓ miR-215	↓ miR-519a	↑ miR-24	↑ miR-193a		
↓ miR-326	↑ let-7i	↑ miR-27a	↑ miR-199a		
Psoriasis[14]					
↓ let-7e	↓ miR-100	↓ miR-197	↓ miR-524	↑ miR-30e-5p	↑ miR-146a
↓ miR-10a	↓ miR-122a	↓ miR-215	↓ miR-5186	↑ miR-31	↑ miR-146b
↓ miR-22	↓ miR-125b	↓ miR-326	↑ miR-17-5p	↑ miR-106a	↑ miR-200a
↓ miR-30c	↓ miR-133a	↓ miR-365	↑ miR-20a	↑ miR-141	↑ miR-203
↓ miR-99b	↓ miR-133b	↓ miR-381	↑ miR-21	↑ miR-142-3p	

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With regard to skin pigmentation disorders, progress has also been made in developing an array of miRNA profiles. For example, Wang et al. examined the miRNA response in peripheral blood mononuclear cells (PBMCs) from patients with vitiligo with and without thymosin-α-1 treatment.[23] Four miRNAs showed altered expression profiles in PBMCs from non-segmented vitiligo patients, which demonstrated an inverted expression pattern post thymosin-α-1 treatment: miR-224-3p, miR-2682-3p, miR-3940-5p, and miR-4712-3p. Interestingly, miR-224-3p and miR-4712-3p have demonstrated oncogenic potential,[24,25] while miR-3940-5p has been reported to act as a tumor suppressor.[26] These findings suggest that cell cycle regulation plays a role in the pathogenesis of vitiligo, and that thymosin-α-1 can effectively reverse the aberration in miRNA expression.

Conclusion

As the technology for detecting the "miRNA signatures" associated with a host of skin conditions becomes more readily available, our knowledge of the critical cellular signaling pathways propagating the symptomologies will be greatly expanded. The information gleaned from these efforts will allow for new diagnostic assays to be implemented and for RNAi-based therapeutics to be designed, developed, and validated. In the very near future, pharmaceutical and skincare products will be marketed for treatment of many skin diseases and disorders that were evolved from the fruit of miRNA profiling projects.

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Conflict of interest

Author declares that there is no conflict of interest.

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