Review Article
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A review on micro RNAs and its application in psoriasis

Abstract

Micro RNA (miRNA) is a non-coding RNA (ncRNA) which was discovered in 1993. It consists of 19-25 nucleotides and it regulates the expression of around 30% of protein coding mRNAs in humans. Recent studies on miRNAs suggest the fact that it has a vital role in the post-transcriptional gene regulation of skin development and in future it can also be used for treating skin diseases. Certain number of novel miRNAs has been identified in skin and various studies were done on the functional roles of miRNAs in psoriasis. In this manuscript, we review the profiling and characterization of miRNAs in the psoriatic skin of humans and discuss its implication in various biological activities and we also share our views on the application of Bioinformatics in predicting novel miRNAs along with the nanotechnology based miRNA delivery to understand the disease pathology of Psoriasis which is followed by treatment. There is a broader scope for addressing the challenges in miRNA based drug delivery in future.

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Harishchander Anandaram,[1] Alex Anand D[2]
[1]Department of Bioinformatics, Sathyabama University, India
[2]Department of Biomedical Engineering, Sathyabama University, India

Correspondence: Harishchander Anandaram, Department of Bioinformatics, Sathyabama University, Chennai, India, Email Harishchander.a@gmail.com

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Introduction

Psoriasis is a chronic and multifactorial autoimmune disorder in skin. In case of Psoriasis there is an abnormal hyper proliferation in keratinocytes, arised due to the activation of T-cells which produces a rich amount of arachidonic acid which leads to generation of various pro inflammatory mediators like PGs, LTs, cytokines and adhesion molecules via MAPK/AP-1, EARK1/2 and protein kinase-C (PKCs) activation pathways.[1] In order to treat Psoriasis there is a need for the incorporation of naturally occuring bioactives like, omega (ω)-3 fatty acids (i.e., EPA and DHA) in a dose dependent manner which results in the inhibition of various pro-inflammatory mediators. Metabolization of EPA and DHA leads to the dampening of inflammation and higher resolution of abnormalities in skin. In case of natural treatment the synthesis of ω-3 PUFA-derived lipid mediators, namely resolvins and protectins have been widely used alone or in combination with other drugs in the treatment. Despite of their meritorious visages, the use of these bioactives is associated with several hiccups like higher range of instability and vulnerable to degradation due to lipid per oxidation. This treatment is also resulted in poor and inconsistent bioavilability by oral and topical administration. The potential use of nanomedicines in the delivery of such bio-actives has gained wider attention owing to their promise in enhancing the characteristics of bioavailability, improved stability and better efficacy. Moreover, barriers in the effective delivery of ω-3 fatty acids and how nanomedicines can be fit in the scope of its therapeutic delivery in psoriasis have also been addressed but it still has a long way to go with multidisciplinary aspects like Pharmacogenomics.

Despite numerous advantages the application of EPA-DHA as ω-3 fatty acids as a therapeutics in the management of psoriasis is still in an initial stage and the approach of nanomedicines to achieve high bioavailability in delivery with safety and stability of ω-3 fatty acids have shown a promising area for the future in psoriasis management. In order to treat psoriasis with respect to genetic approach, a novel fusogenic nucleic acid lipid particle (F-NALP) system containing two therapeutic nucleic acids namely anti-STAT3 siRNA (siSTAT3) and anti-TNF-α siRNA (siTNF-α) were employed along with a novel cationic amphiphilic lipid in oleyl chains were synthesized and used in the nano carrier system and the therapeutic efficacies of F-NALPs were assessed using an imiquimod-induced psoriatic-like plaque model.[2]

In case of treating Psoriasis, a Conventional method of drug delivery systems is inefficient to provide a target effect due to higher bioavailability with its short half life and instability. In such cases a Novel Drug Delivery Systems (NDDS) is required. Certain examples of such systems are liposomes, niosomes, microemulsions, transferosomes, ethosomes, emulsomes, invasomes, dendrimers, nanoparticles, hydrogel, etc.[3–5] A Novel drug delivery system targets the tissues through skin layers and provides a better therapy for topical treatment of psoriasis. Stratum corneum (SC) is the major challenge for the drug to get into the target tissues via skin layers. Penetration enhancers are added in the drug carriers for increasing the penetration capacity of drug through the outermost layer of the skin. The most favorable drug delivery should provide high penetration through SC and should not cause any irreversible changes to the skin barrier.[6–8] Here, the main challenge is to address the transdermal delivery of drugs because there will be a variability in the percutaneous absorption due to site, disease, age and etc. Skin irritation may happen when the toxicities due to drug are more. The first pass metabolic effect of skin is also another challenge for topical delivery.[9–11]

Novel drug delivery systems have lot of advantages. They increase safety and efficacy levels. Drug targeting specificity and lowering systemic drug toxicity are the important merits of NDDS. They also they have the ability to improve absorption rates and will prevent biochemical degradation of pharmaceuticals[12–14] and Skin is mostly considered for the root of drug delivery because it is the largest and outermost organ of the human body. Among three important layers of skin, epidermis functions as a protective barrier of the body.[15–17] There are a lot of blood vessels and layers present in the epidermis. Sub layers are also present in this outermost layer such as stratum lucidum, stratum corneum, stratum spinosum, stratum granulosum, and stratum germinativum. Dermis is present beneath the outermost layer, which is composed of connective tissues.[18,19] Hypodermis is situated under the dermis layer. For the treatment of psoriasis, percutaneous absorption of drugs is one of the widely accepted ways of drug delivery. The challenge that offered by topical treatment is the presence of SC as a barrier.[20–22] Conventional forms of drug

delivery through skin have come across with many side effects and other application difficulties. Disruption of SC and targeting to the deeper layers of skin are not possible with ointments, creams etc. So, novel dermal delivery systems help to overcome these limitations, thereby enhance the bioavailability and potential of drug and are widely used for the treatment for psoriasis recently.[23,24] Since, Skin is the largest organ of humans which regenerates throughout the entire life of every individual and serves as an outermost barrier for preventing the internal organs from dehydration.[25,26] It has a system for maintaining the regulatory mechanism of mediators with local or systemic effects.[27–29] As a common skin disease, psoriasis is chronic, auto immune and a complex genetic disorder which affects around 2% of world population. Psoriatic skin contains certain symptoms of inflammation which are raised as scaly lesions.[30–32] There are three types of cellular alterations in psoriatic skin i.e. abnormal differentiation of keratinocyte, hyperproliferation of keratinocyte and infiltration of immune cells.[33] Studies on the molecular components and cellular pathways of inflammation are one of the major contributions to understand the pathogenesis of psoriasis.[24–37] The interplay between the genetic and environmental factors influence the onset and progression of psoriasis.[38,39] Recent studies on miRNAs, illustrate the fact that it is a novel regulator of gene expression and it plays a vital role in psoriasis.

Maturation of miRNAs involves multiple steps and initially two intermediate forms of miRNAs, primary (pri-) and precursor (pre-) miRNAs, are produced sequentially. In this process, RNase III enzyme Drosha and partner double-stranded RNA (dsRNA) binding protein Dgcr8 cleave pri-miRNAs to produce hairpin-shaped pre-miRNAs that are recognized by Exportin5 and are subsequently transported from nucleus to cytoplasm. There is another RNase III enzyme called Dicer which cleaves the pre-miRNAs to release ~22-nt double-stranded RNA duplexes (namely miRNA/miRNA* duplexes) with ~2-nt 3' overhangs. One strand of a RNA duplex is termed mature miRNA which is further loaded into an Argonaute protein in the RNA-induced silencing complex (RISC) to exert its regulatory function on the basis of its binding with the target transcripts.[40,41]

Since there present there is no permanent cure for Psoriasis in Current stage, we analyze the inflammatory response by the scaly lesions with a widely aberrant gene expression.[42] Psoriasis was thought to be initiated by the complex interactions between environmental and genetic factors. Skin lesions in Psoriasis are characterized by the hyperproliferation and aberrant differentiation of keratinocytes by the process of in filtering the inflammatory cells into the dermis and epidermis.[43] Psoriasis skin lesions are characterized by hyperproliferation and aberrant differentiation of keratinocytes and infiltration of inflammatory cells into the dermis and epidermis. Recent studies on the increase or decrease in the gene expression levels of patients with psoriasis, revealed the fact that miRNAs play critical roles in regulating as a class of post transcriptional genes in Psoriasis.[44] Micro RNA is a family of non coding RNA (ncRNA) which was discovered in 1993, it consist of 19-25 nucleotides and regulates the expression of approximately 30% of protein-coding miRNAs in humans. Base pairing at the position 2–8 nucleotides ehich are relative to the 5' end of the small RNA is termed as the "seed" region and it appears to be important for target recognition.[45,46]

A unique miRNA can regulate the expression of hundreds of proteins and the expression of a specific protein may be controlled by several miRNAs.[47] The sequence conservation of most miRNAs lies between the distantly related organisms to suggest the impact of a strong evolutionary pressure[48] and they have been shown to participate in many fundamental life processes like development, differentiation, organogenesis, growth control and apoptosis. Accordingly, deregulation of miRNA expression has been shown to contribute to cancer, heart diseases, infectious diseases, inflammatory diseases, and other medical conditions, making them potential targets for medical diagnosis and therapy.[49] Initially, Lee et al.,[50] had found lin-4 as a regulator of developmental timing in nematode Caenorhabditis elegans.[50] After several years, Reinhart et al. had discovered lethal-7 (let-7) gene in Caenorhabditis elegans.[51] At present, 2500 miRNAs are in the human genome. Majority of miRNA are intragenic.[52] Micro RNAs are initially transcribed as part of an RNA stem-loop that in turn forms part of a several hundred nucleotides long miRNA precursor miRNA (pri-miRNA).[53]

Mature miRNA is a part of an RNA-induced silencing complex (RISC) which contains Dicer and many associated proteins.[53,54] Since miRNA is involved in the functioning of eukaryotic cells, dysregulation of miRNA been associated with disease and a miR2Disease database contain documents with known relationships between miRNA dysregulation and human disease.[55] Micro RNAs can bind to target messenger RNA (mRNA) transcripts of protein-coding genes and negatively control their translation or cause mRNA degradation and the key factor is to identify the importance miRNA target with accuracy. A detailed review for the advances in the miRNA target identification methods and available resources has been published by Zheng et al.[50]

Next-Generation sequencing (NGS) is a sequencing technology with the incorporation of high-throughput methods which has the capability of profiling the expression of various RNA in different species with a resolution of single-nucleotide on the basis of genome-wide scaling.[56–58] NGS sequences RNA transcripts directly and hence it is able to facilitate the *de novo* discovery of genes with novel miRNA.[59,60] Recent studies on NGS had discovered a pool of miRNAs and miRNA-like RNAs on the basis of their variants. These diverse miRNAs include canonical and noncanonical miRNAs,[61–64] miRNA-like RNAs,[65–69] and miRNA isoforms.[70,71] Canonical miRNAs are generated from a biogenesis pathway that requires Drosha and Dicer. Noncanonical miRNAs are produced from alternative pathways in biogenesis where Drosha is not involved. The first example of noncanonical miRNA is the class of mirtrons, which arise from a short nucleotide of sequence length renges from 60 to 100 bases. Dicer dependent but Dgcr8 independent miRNA-like RNAs can also arise from the formation of local hairpin within the region of larger noncoding RNA (ncRNA). Micro RNAs are typically defined as the most abundant small RNAs on pre-miRNA hairpins. Nevertheless, other less abundant but cognate small RNAs from the same pre-miRNAs, which differ by a few bases from miRNAs, have also been reported[72,73] and the variants of these miRNA have been named as *isomiRs*.[73,74] *IsomiRs* can function as regular miRNAs[75,76] and they often share the mRNA target which is common with their companion miRNAs but in some cases they may also have their own exclusive genes as target.[77] The emergence of such diverse miRNAs as additional regulators of gene expression with potential functions is complementary to that of canonical miRNAs which reflects the robustness and plasticity of miRNA-mediated regulation of gene expression.

There is an estimate that miRNAs regulate over the one-third portion of protein-encoding mRNAs in humans.[78,79] Recent studies on the development of mammalian skin have revealed the fact that that "Interaction between miRNAs and their target mRNAs is vital for the regulating signaling pathways during cell differentiation".[80,81] There

were also reports on Noncanonical miRNAs, miRNA-like RNAs and isomiRs in normal and psoriatic skin of human.[82] Dysregulation of miRNAs and their regulated targets has been implicated in the pathogenesis of psoriasis[83–85] as well as other forms of disorder of the skin, including malignant melanoma.[86–88] The aberrant expression of small noncoding RNAs in psoriatic skin has suggested functional roles of sncRNAs in psoriasis. This emerging theme on miRNAs suggests that these miRNAs have the potency to become a therapeutic target for treating psoriasis.

Role of micro RNAs in skin development

A Significant progress has been made in identifying and characterizing miRNAs along with their specific functions in morphogenesis and homeostasis of skin. Certain miRNAs with those functions are studied and the list is given in Table 1. In case of psoriasis, it has been revealed that the up-regulation of miR-203 in psoriatic skin is implicated in targeting suppressor of a signaling molecule called cytokine Signaling 3 (SOCS3).[89,90] Further, hsa-miR-203 has been characterized as an inhibitor of cell proliferation on the basis of its targeting action on *p63* (transcription factor) in normal skin. Hence, there is an argument for the state of down regulated miR-203 in psoriatic skin. It has also been observed that has-miR-146a is up regulated in the lesions of psoriatic skin and patients suffering from rheumatoid arthritis.[51,52] Micro RNA, hsa-miR-146a is involved in the pathway of TNF-α by targeting the TNF receptor-associated factor 6 (TRAF6) and IL-1R-associated kinase (IRAK), which play a major role in the inflammation of psoriatic skin inflammation. On the basis of gene expression pattern it was found that has-miR-146a is a dependent factor of NFκB.[53–55] Further, it has been found that the activation of NFκB leads to inhibition of TNF-α-induced apoptosis, which may be regulated by the over expression of miR146a and hence it can potentially contribute to the pathogenesis of psoriasis.[55,56] In contrast, hsa-miR-125b is down-regulated in psoriasis and it is involved in post-transcriptional repression of TNF-α. In cases of the down-regulation of has-miR-125b, the inhibitory effect on TNF-α is reduced and it may contribute to an increased expression of TNF-α in the lesions of psoriatic skin and targeting these specific miRNAs may be a promising therapy for psoriasis in future. In case of 5' isomiRs, many studies are lacking to understand the level of miRNA expression in skin and its impact on mRNA expression. Recent studies have investigated a few cases of 5' isomiRs[90] and it has been identified that showed 5'-isomiRs of hsa-miR-223 have an exclusive targets in neutrophils and the existing experimental evidence from the assays of *in vitro* target cleavage indicate the fact that that has-miR-142-5p and its 5'-isomiR have diverse specificity of target.[91] Hence, on the basis of an assumption that that 5'-isomiRs are functional, the dysregulated 5'-isomiRs, including those from the loci of an abundantly expressed hsa-miR-203, hsa-miR-142 and hsa-miR-223 are also of a particular interest in psoriatic skin.

Table 1 Functions of miRNAs in skin development

Micro RNAs	Functions	References
hsa-miR-203	Induced in supra basal layer for inhibiting the process of cell proliferation by repressing *p63* and regulates the process of transition from a basal layer to its supra basal layer in the epidermis.	Larsen et al.[94]
hsa-miR-34 a/c	Repression of *p63* in epidermal cells to maintain the progression of cell cycle and expression of cyclin D1 and Cdk4.	Antonini et al.[100]
hsa-miR-125b	Expressed in the stem cells of skin to balance the process of commitment in self-renewal And early lineage.	Zhang et al.[46]
hsa-miR-200	Maintains the proliferation of Progenitor cells in the basal layer of skin.	Wang et al.[50]
hsa-miR-205	Maintains the transition of epithelial-mesenchymal in basal layer of skin.	Park et al.[95]

Enrichr

Enrichr is an interactive tool for enrichment analysis of gene list. Enrich R is one of the most powerful methods for analyzing the massive datasets and producing the results with the list of differentially expressed genes.[92,93] In EnrichR, Differentially expressed gene lists are extracted from RNA-seq or microarray studies; gene lists can be created from genes by analyzing the mutations in cohorts of patients, or gene lists which can become a putative target of transcription factors or histone modifiers, as profiled by ChIP-seq. In fact, gene lists can be produced from any relevant experimental method that profiles the entire genome or the proteome. Once unbiased lists of genes or proteins are generated from such experiments, these lists are used as input for computing an enrichment with the existing lists which was created from prior knowledge which was organized into gene-set libraries. Gene-set libraries are used for organizing the accumulated knowledge about the function of a gene cluster.

Each library of a gene-set is made of a set of related genes where each set of a gene is associated with a functional term such as a pathway name or a transcription factor that regulates the genes. In order to create such gene-set libraries, assembling of gene sets from diverse contexts. The original method which was developed in this approach is called as the gene set enrichment analysis (GSEA), at first stage it was used to analyze microarray data which was collected from the muscle biopsies of diabetic patients[94] on the basis of the outcomes obtained from Kolmogorov-Smirnov test. It predicts the miRNA regulated association with the gene list on the basis of standard deviation between the differentially expressed genes and their collective functions in mammals[95] and the authors of EnrichR have also developed a database called MSigDB with the collection of pre defined libraries in a gene-set.[96] However, most of the enrichment analysis tools focus on performing enrichment using only the Gene Ontology resource.[97] Besides the computing of enrichment for the input lists of genes, gene-set libraries can be used to build a network to illustrate the functional association.[98] Apart from that EnrichR predicts the novel functions for genes and discover a distal relationship between the biological and pharmacological processes. While many gene-set libraries and tools were already exist, visualization of enrichment results can be done in more intuitive and interactive ways.

Enrichr is an integrative mobile and web-based software application which includes new gene-set libraries with a new approach to rank enriched terms and enhances a powerful and interactive visualizations of the results in new ways. Enrichr is delivered as an HTML5 web-based application and also as a mobile app for the iPhone, Android and Blackberry. Users are provided with the ability to share the results with collaborators and export vector graphic figures that display the enrichment results in a publication ready format. The ability of Enrichr was evaluated to rank terms from gene-set libraries by comparing the

Fisher exact test to a method developed on the aspect of computation for identifying the level of deviation from the expected rank of terms. To evaluate various methods that rank enriched terms, analysis was done from the list of differentially expressed genes from studies that measured gene expression after knockdown of transcription factors to see the ranking of the knocked down factors using a transcription-factor/target-gene library.[99,100]

Mirmap

MiRmap software identifies the number of miRNA binding sites in a gene (mRNA).This software allows us to examines the feature correlation which is based on experimental data resulted from the high throughput techniques of immune purification, transcriptomics and proteomics.[101] Overall, accessibility of target site appears to be the most predictive feature of miRmap. Mirmap is implemented as an open-source Python library with a comprehensive range of features using thermodynamic, probabilistic, evolutionary and sequence-based approaches to rank potential miRNA targets using information beyond the seed match.

Application of bioinformatics in identifying novel miRNAs to treat psoriasis

Various bioinformatics programs were used for predicting novel miRNAs in Psoriasis using seed match approach and network approach. Target Scan Version 6.2 is an online server which predicted hsa-miR-133a and hsa-miR-133b are associated with the gene ABCC1 and it may be a possible therapeutic target of Psoriasis and it was followed by the analysis of miRmap, which analyses the possible binding of miRNA with mRNA of gene has predicted hsa-miR-370, hsa-miR-3074-5p and hsa-miR-4756-3p are associated with the gene FCGR3A could be a possible therapeutic target for Psoriasis.[102] Similarly miRtarbase has predicted the associations of hsa-miR-365a-3p with the gene IL6; hsa-miR-7-5p with the gene ABCC1 and has-miR-520h with the gene ABCG2, in case of miRtarbase certain experimental evidences were present for the miRNAs which targets the associated genes of Psoriasis.[103] In case of biomarker research, TargetScan and miRmap software had predicted that hsa-miR-520d-5p and has-miR-524 is associated with the psoriasis related gene TRAF3IP2. In addition to the above mentioned resources for identifying the predicted and validated miRNAs, current research in Psoriasis focus on identifying miRNAs which targets more than 3 or 4 genes which are associated with Psoriasis because those miRNAs have a maximum probability to become a therapeutic target for Psoriasis in future. Network analysis of miRNAs in Psoriasis is obtained from EnrichR[104–108] and it was predicted that hsa-miR-18a-3p has a maximum probability to become a therapeutic target for Psoriasis.

Future prospective and further challenges

Though certain studies were carried out on miRNAs in the skin of mammals, the proof of significance into an insight of the novel layer of gene regulation require an in depth analysis and the knowledge about the aberrant expression of small noncoding RNAs in psoriatic skin has laid a foundation for understanding the roles of miRNAs and endo-siRNAs in psoriasis. At Present have a good collection of miRNAs as well as their validated and putative targets but understanding the complex genetic networks that act as a pillar in the etiology of autoimmune based skin disorders such as psoriasis requires a deeper study of disease pathology and the challenge is to build high-quality regulatory network for explaining the factors involved in the disease pathology of psoriasis. In Future, we require a collective effort from the research community in the area of miRNA based therapeutics to treat Psoriasis with small RNA-based therapies.

Conclusion

On the basis of sequence based computational analysis our analysis in Target Scan, it was found that hsa-miR-370, hsa-miR-3074-5p and hsa-miR-4756-3p of FCGR3A and similarly hsa-miR-3163 and hsa-miR-4496 of ABCG2 contain more than 2 mRNA binding sites and hence the above mentioned miRNAs have a maximum chance to become a therapeutic target for Psoriasis. Similarly, Mir Tar Base identifies certain novel miRNAs for Psoriasis and they were hsa-miR-365a-3p of IL6, hsa-miR-7-5p of ABCC1 and hsa-miR-519c-3p, hsa-miR-520h of ABCG2 and on the basis of probability these miRNAs have a maximum chance to become a therapeutic target of Psoriasis. In accordance with MiRbase hsa-miR-365a-3p of IL6, hsa-miR-7-5p of ABCC1 and hsa-miR-519c-3p, hsa-miR-520h of ABCG2 contain two binding sites in Mir map and on the basis of probability these miRNAs also have a chance to become a therapeutic target of Psoriasis. Finally the network analysis of EnrichR confirms the fact that hsa-miR-19a-3p and miR-19a-5p has the maximum potential to become a biomarker for Psoriasis because it binds the mRNAs of 7 genes (CAST, TSC1, SPATA2, ERAP1, TNIP1, ERBB3 and SDC4) which are associated with Psoriasis. Whereas, hsa-miR-19b-5p bind only with the mRNAs of 5 genes (CAST, TNIP1, IL23R, TSC1and TRAF3IP2) which are associated with Psoriasis. In future, the regulatory mechanisms of hsa-miR-19a-3p and hsa-miR-19a-5p will be addressed for the identification of its impact on the signaling pathways of Psoriasis. There were also several other methodologies for analyzing the target dynamics of miRNA in the process of multiple mRNA selection on the basis of seed pairing. In order to understand the complete mechanism of miRNA dynamics, simulation methods like monte-carlo and constrained molecular dynamics is required but those methodologies are beyond the scope of our present investigation. In future, all the above mentioned methodologies will be utilized for identifying novel miRNAs which could be a probable therapeutic target for other autoimmune diseases.

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Conflict of interest

The author declares no conflict of interest.

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