Frontiers in Health InformaticsISSN-Online: 2676-7104 www.healthinformaticsjournal.com
2025; Vol 14: Issue 2 Open Access

Identification Of Mir-103a/PLEKHA1 Pair As Candidate Biomarkers And Therapeutic Targets For Skin Aging By Bioinformatics Analysis

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Cite this paper as: Silvia Clarina, Ferbian Milas Siswanto, Ian Pranandi, Maria Dara Novi Handayani, Rita Dewi, Regina (2024), Identification Of Mir-103a/PLEKHA1 Pair As Candidate Biomarkers And Therapeutic Targets For Skin Aging By Bioinformatics Analysis. *Frontiers in Health Informatics*, *14(2) 2245-2254*

Abstract: Introduction: Skin aging is a deterioration in function and structure of the skin that occurs due to various factors. It is an intricate process involving several mechanisms. Identification of skin aging biomarkers is critical for early diagnosis and development of therapeutic targets.
Objectives: This study aims to identify gene molecular links related to skin aging using an in-silico approach.
Methods: The expression profiling by array and high throughput sequencing of GSE55299, GSE72264, GSE152251, GSE83922, GSE169382, and GSE240226 datasets were retrieved from the Gene Expression Omnibus (GEO). The data were integrated and analyzed to identify the differentially expressed microRNA (DEMs) and mRNA (DEGs) in skin aging. Fold changes (FCs) in the expression of individual genes were calculated with cut-off value of $p \leq 0.05$ and $FC \geq 1.5$. Data were processed to determine miRNA and mRNA hub which were then predicted using GeneCards and TargetScan.
Results: Eight genes and two miRNAs experienced alteration in expression in mRNA and miRNA data sets, respectively. In individuals with aging skin, miR-103a expression was downregulated and PLEKHA1 expression was upregulated, respectively. The intersection of DEMs and DEGs predicted targets resulted in one miRNA-mRNA pair related to skin aging, miR-103a / PLEKHA1. Additionally, bioinformatic analysis indicated that PLEKHA1 was a target of miR-103a.
Conclusions: This study uncovered miR-103a / PLEKHA1 pair potentially linked to the progression of skin aging, offering fresh insights into the molecular mechanisms underlying the condition, potential biomarker and therapeutic target.
Keywords: genes, in silico, microRNA, skin aging

1. Introduction:

Skin serves as a protective barrier while regulating temperature and sensory perception. It consists of three main

layers, the epidermis, dermis, and subcutaneous tissue, each playing a vital role in maintaining skin health. As we age, structural and functional changes occur in these layers, leading to visible signs of aging such as wrinkles, sagging, and dryness [1]. The aging process is influenced by both intrinsic factors, such as genetics and natural biological changes, and extrinsic factors, including sun exposure, pollution, and lifestyle [2]. Over time, collagen and elastin production decline, reducing the firmness and elasticity of the skin. Additionally, slower cell turnover and decreased moisture retention contribute to a dull and rough texture [3–5]. The successful aging paradigm emphasizes health and active engagement in life, challenging traditional views of aging as a period dominated by illness. This concept is increasingly linked to reducing visible signs of aging on the skin. In this context, preventative aesthetic dermatology can support healthy aging by addressing or preventing specific skin conditions and slowing the aging process. This approach integrates local and systemic therapies, advanced instruments, and invasive procedures to achieve its goals [6].

Due to a complicated nature of pathways involved in skin aging, many studies have explored the most critical mechanisms underlying skin aging that could be accurately used as biomarker(s) and therapeutic target(s). Moreover, the late identification of skin aging often reduces the effectiveness of existing treatment options. The absence of specific molecular markers for early detection and prognosis presents a major challenge in addressing skin aging [7]. Understanding the mechanisms behind the skin aging process is essential for developing effective strategies to address age-related skin changes. This insight is highly valuable for advancing research and innovation in the field of dermato-cosmetics [6]. Delineating the molecular mechanisms and biomarker identification involves a broad spectrum of molecular, genetic, or biochemical indicators [8]. Recent advancements in -omics technologies offer potential for discovering promising biomarkers linked to skin aging. These biomarkers provide crucial insights into the mechanisms and progression of pathological conditions, enabling clinicians to make personalized treatment [9].

MicroRNAs (miRNAs) are gaining recognition as key regulators of aging and longevity. These short noncoding RNAs, typically 19–22 nucleotides long, bind to the untranslated region (UTR) of target mRNAs, often inhibiting translation or triggering mRNA degradation [10–12]. MiRNAs play crucial roles in regulating the balance between proliferation and replicative senescence [13]. In the context of skin aging, certain miRNAs are primarily observed in keratinocytes, dermal fibroblasts, and melanocytes during replicative senescence [14]. Exploring the regulatory functions of miRNAs in skin aging could provide insights into their potential for novel therapeutic applications. However, despite many studies on miRNA expression and function in skin aging, comprehensive analyses of the miRNA–mRNA regulatory network in skin remain relatively rare.

OBJECTIVES

In this study, we aimed to identify miRNAs and genes that are potentially related to skin aging by using in silico approach. The identified molecular interactions are expected to contribute to understanding the pathophysiological processes underlying skin aging that could potentially be used as biomarkers and therapeutic targets for preventing skin aging.

METHODS

MiRNAs and mRNAs associated with skin aging were identified by entering the keywords "skin aging," "miRNA," and "mRNA" into the NCBI Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). The selected datasets were miRNA expression data (GSE55299,

GSE72264, GSE152251) and mRNA expression data (GSE83922, GSE169382, GSE240226), which were downloaded and further analyzed. The miRNA profile from the GSE55299 dataset contains miRNA expression data from fibroblasts derived from young and old groups, measured using the Affymetrix Multispecies miRNA-2 Array. The GSE72264 includes miRNA expression data from dermal tissue samples of 6 healthy elderly (>60 years old) and 6 healthy young (<10 years old) individuals, measured using the Agilent-031181 Unrestricted_Human_miRNA_V16.0_Microarray. The GSE152251 contains miRNA expression data from exosomes in two groups (control and UVB-exposed melanocyte), measured using the Illumina HiSeq 4000. The mRNA profile from the GSE83922 dataset contains gene expression from melanocyte samples derived from 4 young and 4 elderly individuals, measured using the Affymetrix Human Gene 1.1 ST Array. The GSE169382 contains gene expression data from melanocyte samples in control groups and groups exposed to UVA and UVB, measured using the Illumina HiSeq 2500. The GSE240226 contains gene expression data from Human Dermal Fibroblast (HDF) samples from control and UVA-exposed groups, measured using the Illumina NovaSeq 6000.

All datasets were processed using an interactive built-in application called GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/). Differentially expressed miRNAs (DEMs) and differentially expressed genes (DEGs) were filtered using criteria of an adjusted false discovery rate (FDR) ≤ 0.05 and a fold-change (FC) ≥ 1.5 as the screening threshold for each group. DEMs and DEGs from each dataset were visualized using volcano plots and Venn diagrams using SRplot (https://www.bioinformatics.com.cn/srplot). The predicted target genes of the intersecting miRNAs were analyzed using MirTarBase (https://mirtarbase.cuhk.edu.cn/), ENCORI (https://rnasysu.com/encori/), and MirTargetLink (https://ccb-compute.cs.uni-saarland.de/mirtargetlink2) and then searched for the intersection with Volcano plot. The potential miRNA-mRNA pair were then predicted using Venn diagram to identify miRNA(s) that target skin aging gene(s). The identified pair were then analyzed using GeneCards (https://www.genecards.org) and TargetScan (https://www.targetscan.org/vert_80/) to obtain information on the molecular functions and the binding mode, respectively. The flowchart of this study is presented in Figure 1.

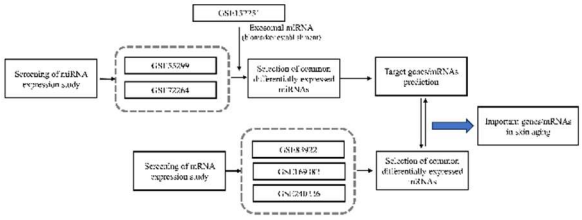

Fig. 1. Flowchart of the present study.

RESULTS

Identification of DEMs in Skin Aging

A total of 15 DEMs were identified in GSE55299, including 4 upregulated miRNAs and 11 downregulated miRNAs (Fig. 2a). In GSE72264, 116 DEMs were identified, including 46 miRNAs with decreased expression and 70 miRNAs with increased expression (Fig. 2b). A Venn diagram visualization was then conducted, revealing 6 overlapping miRNAs between the two datasets: miR-645, miR-154, miR-103, miR-30a, miR-602, and miR-557 (Fig. 2c). To identify potential biomarkers from these miRNAs for clinical applications, further

analysis was performed with the GSE152251 dataset, which represents exosomal miRNAs. In this analysis, miR-154a-5p and miR-103a-3p were identified, both showing decreased expression (Fig. 2c). Next, the potential target genes for both miR-103a-3p and miR-154a-5p were assessed using MirTarBase, MirTargetLink, and ENCORI, and visualized with a Venn diagram. The data revealed a total 25 and 335 predicted target genes for miR-154a-5p and miR-103a-3p, respectively (Fig. 2d and 2e).

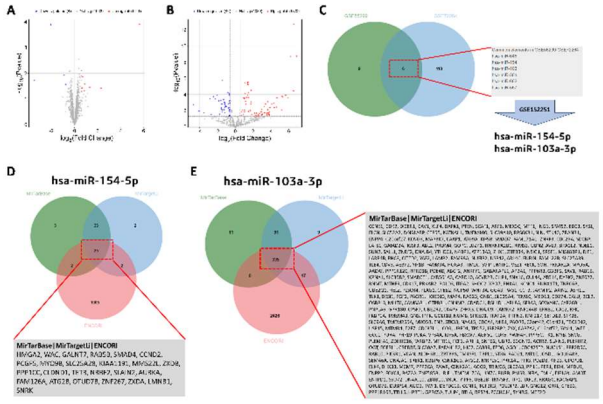

Fig. 2. Differentially expressed miRNAs in skin aging datasets. Volcano plot of differentially expressed miRNAs in GSE55299 (a) and GSE72264 (b) datasets. Upregulated miRNAs are shown in red, and downregulated miRNAs are shown in blue. (c) Overlapping differentially expressed miRNAs among two GEO datasets represented through a Venn diagram and further intersected with DEMs from GSE152251 dataset. Predicted gene targets of miR-154a-5p (d) and miR-103a-3p (e) were identified using MirTarBase, MirTargetLink, and ENCORI and Venn diagram was used to identify the intersection of all predicted target genes.

The mRNA Expression Profile Related to Skin Aging

The expression of 717 genes were altered in the GSE83922 dataset, including 388 upregulated genes and 329 downregulated genes (Fig. 3a). In the GSE169382 dataset, 367 genes experienced changes expression, comprising 91 genes with decreased expression and 276 genes with increased expression (Fig. 3b). In the GSE240226 dataset, 2969 genes had differential expression, including 892 genes with decreased expression and 2077 genes with increased expression (Fig. 3c). To identify overlapping DEGs among the three mRNA datasets, a Venn diagram analysis was conducted, revealing 8 genes with altered expression in all datasets. These genes include PLEKHA1, HCP5, IFITM1, SERPINB2, OAS2, IFI6, MX1, and OAS1 (Fig. 3d).

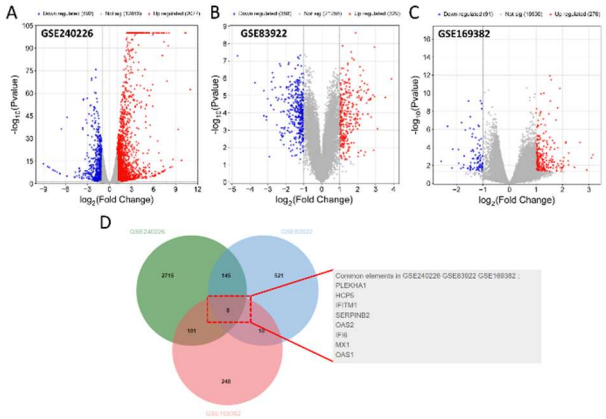

Fig. 3. Differentially expressed mRNAs in skin aging datasets. Volcano plot of differentially expressed mRNAs in GSE240226 (a), GSE83922 (b), and GSE169382 (c) datasets. Upregulated mRNAs are shown in red, and downregulated mRNAs are shown in blue. (d) Overlapping differentially expressed mRNAs among three GEO datasets represented through a Venn diagram.

Correlation Between DEMs and DEGs in Skin Aging

In general, miRNAs function as negative regulators of gene expression by binding to and inducing the degradation of mRNA. This study focuses on DEGs with consistently increased expression in skin aging. Venn diagram analysis revealed one overlapping gene, PLEKHA1, which was a predicted target of miR-103a-3p (Fig. 4a). An analysis of the human PLEKHA1 3' UTR region using TargetScanHuman 7.2 identified a binding region for miR-103a-3p in the conserved part of the PLEKHA1 3' UTR, with a perfect match at positions 2–8 of the miRNA seed region (Fig. 4b). According to genome-wide association studies (GWAS) data downloaded from GeneCards, PLEKHA1 is associated with the risk of several pathological conditions, including aging, with a GWAS score of 7.4 (Fig. 5a). Based on these results, a model was developed showing that aging leads to decreased expression of miR-103a-3p, resulting in increased levels of PLEKHA1 (Fig. 5b).

Fig. 4. Identification of miRNA-mRNA pair. (a) Volcano plot of potential target genes of miR-154a-5p and

miR-103a-3p, and the DEGs identified the potential pair of miR-103a-3p / PLEKHA1. (b) Analysis of miR-103a target site(s) in PLEKHA1 gene. TargetScan bioinformatics algorithm for predicting miRNAs targeting the first 1500 bp of the PLEKHA1 3' UTR.

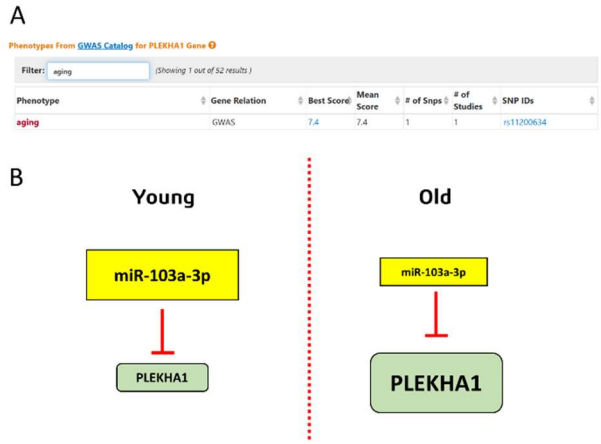

Fig. 5. Schematic model of factors regulating skin aging. (A) Function of PLEKHA1 based on GWAS data. (B) In young skin cells, the expression of PLEKHA1 is relatively low due to the suppressing effects of miR-103a-3p. In older skin tissue, the reduced levels of miR-103a-3p lead to the accumulation of PLEKHA1, resulting in the aging phenotypes of skin tissue.

DISCUSSION

Many studies have discussed biomarkers of skin aging [15]; however, few have focused on the miRNA and gene pair(s). In the present study, using various databases and comprehensive analysis, we identified intersecting miRNAs and mRNAs in skin aging datasets. These findings confirm the existence of molecular relationships that have the potential to serve as biomarkers for skin aging. To the best of our knowledge, this is the first study to identify miRNA-mRNA pair and their roles in skin aging using an in-silico approach.

MicroRNAs belong to a class of non-coding RNAs that suppress gene expression by inhibiting protein translation or initiating mRNA degradation [16]. Changes in miRNA expression result in altered gene expression profiles, involving a series of biological processes that contribute to various molecular pathways, including skin aging. In fact, the role of miRNAs in regulating skin development and maintaining homeostasis has begun to emerge in recent years. Many studies have reported that various microRNAs exhibit inverse expression across various age groups, indicating their involvement in regulating age-related signaling pathways. Research has also highlighted differentially expressed miRNAs during both chronological aging and photoaging of the skin. While some studies have suggested miRNA-mediated mechanisms regulating senescence in specific skin cells, discrepancies in the findings remain. The role of miRNAs in controlling skin senescence and aging is not yet fully understood, hindering progress in the development of anti-aging therapies [14,17].

To comprehensively study the role of miRNA in skin aging and identify the critical miRNA-mRNA pair(s), we conducted bioinformatics experiment using freely available transcriptomic datasets. We found that miR-103a-3p expression decreases in older groups, suggesting its potential role in molecular pathways that mitigate the risk of skin aging. To the best of our knowledge, the role of miR-103a-3p in skin aging is unknown.

Experimental studies have demonstrated its involvement in degenerative diseases such as Alzheimer's, osteoarthritis, infertility, diabetes mellitus, obesity, Parkinson's disease, myocardial ischemia, and various cancers [18]. In skin tissues, miR-103a-3p has been implicated in atopic dermatitis and melanoma. In atopic dermatitis, hsa-miR-103a-3p expression is significantly higher in serum and contributes to inflammation by reducing arginine methyltransferase 5 (PRMT5) protein expression and demethylation of GATA3 arginine residues [19]. In melanoma, miR-103a-3p inhibits C1QB, promoting malignant behaviors such as proliferation, migration, and invasion of melanoma cells. Its role in promoting proliferation suggests that decreased miR-103a-3p levels may be indirectly linked to skin aging, as epidermal thinning—caused by reduced proliferation and renewal capacity of basal keratinocytes and a decline in epidermal stem cell numbers—is a hallmark of skin aging [20].

Oxidative stress from endogenous and exogenous sources is another widely studied hallmark of aging, including skin aging. Oxidative stress, through oxidative damage to macromolecular cellular components and the extracellular matrix of the skin, exacerbates skin aging, resulting in uneven skin tone, wrinkles, sagging, dryness, and roughness [21]. MiR-103a-3p, by targeting high mobility group box 1 (HMGB1), reduces interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and malondialdehyde (MDA), while increasing superoxide dismutase (SOD) levels [22,23]. By activating antioxidant systems, miR-103a-3p may prevent skin aging, and its decline with age could lead to the clinical symptoms of skin aging [22]. Although research on the role of miR-103a-3p in skin aging is still limited, this study, combined with theoretical literature, can serve as a foundation for future experimental or observational studies to confirm its potential as a skin aging biomarker.

This study also identified PLEKHA1 as one of the eight DEGs intersecting among the three datasets, which is a target gene of miR-103a-3p. The role of PLEKHA1 in skin aging has not yet been validated. In cells, PLEKHA1 localizes to the plasma membrane, where it binds phosphatidylinositol 3,4-bisphosphate (PtdIns3,4P2). Due to its localization, PLEKHA1 is implicated in forming signaling transduction complexes at the plasma membrane. To date, PLEKHA1 has been associated with the pathogenesis of macular degeneration, osteoporosis, diabetes mellitus, and Alzheimer's disease—degenerative conditions with increased risks as people age [24–26]. In vitro and in vivo studies showed that PLEKHA1 is involved in cytoskeletal rearrangement in B cells [27]. Cytoskeletal rearrangement during aging is linked to degenerative diseases such as cancer, vascular diseases, and neurodegenerative conditions [28]. Furthermore, research has demonstrated that PLEKHA1 can induce oxidative stress, particularly in diabetic nephropathy [29], aligning with the theory that miR-103a-3p inhibits oxidative stress. Based on these two hypotheses, low miR-103a-3p and high PLEKHA1 levels during aging may induce oxidative stress and damage.

Regarding skin aging, a genome-wide siRNA-based functional genomics study in human melanocyte cultures reported that PLEKHA1 knockdown using siRNA reduced the expression of microphthalmia-associated transcription factor (MITF), tyrosinase, and melanin protein levels [30]. This indicates that increased PLEKHA1 during aging may upregulate tyrosinase and melanin expression, leading to hyperpigmentation. Overall, the role of PLEKHA1 in skin tissue remains largely unexplored, leaving significant potential for future experimental studies. To our knowledge, this is the first study to identify the diagnostic potential of PLEKHA1 in skin aging.

The limitation of this study is that the reported results are bioinformatic predictions based on non-Indonesian populations. Thus, clinical research on Indonesian populations with a sufficiently large sample size is needed to validate the hsa-miR-103a-3p and PLEKHA1 pair in skin aging. Additionally, in silico study possess another limitation in which the model is simplified for simulations, which may produce results that do not fully represent

the complexity of natural conditions. To this end, further experimental studies are required to validate this pair for the development of diagnostic tools and therapeutic targets for skin aging.

CONCLUSION

In the present study, we obtained molecular information related to skin aging. Analysis of DEMs in three miRNA datasets (GSE55299, GSE72264, and GSE152251) identified two miRNAs, miR-154-5p and miR-103a-3p, that showed decreased expression in aging skin. Analysis of DEGs in three mRNA datasets (GSE83922, GSE169382, and GSE240226, GSE169382, and GSE240226) identified PLEKHA1 as the only DEGs in skin aging that is potentially regulated by miR-103a-3p. The miR-103a-3p/PLEKHA1 pair represents a potential biomarker and predictor of skin aging that could be utilized to improve early diagnostic strategies.

ACKNOWLEDGMENTS

This study was supported by Hibah Dosen Pemula Unika Atma Jaya (Grant No. 162.24/III/LPPM-PM.10.01/02/2024).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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