



Current insight into the roles of microRNA in vitiligo

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Abstract

Vitiligo is a common chronic depigmented skin disease characterized by melanocyte loss or dysfunction in the lesion. The pathogenesis of vitiligo has not been fully clarified. Most studies have suggested that the occurrence and progression of vitiligo are due to multiple factors and gene interactions in which noncoding RNAs contribute to an individual's susceptibility to vitiligo. Noncoding RNAs, including microRNAs (miRNAs), are a hot topic in posttranscriptional regulatory mechanism research. miRNAs are noncoding RNAs with a length of approximately 22 nucleotides and play a negative regulatory role by binding to the 3'-UTR or 5'-UTR of the target mRNA to inhibit translation or initiate mRNA degradation. Previous studies have screened the differential expression profiles of miRNAs in the skin lesions, melanocytes, peripheral blood mononuclear cells (PBMCs) and sera of patients and mouse models with vitiligo. Moreover, several studies have focused on miRNA-25, miRNA-155 and other miRNAs involved in melanin metabolism, oxidative stress, and melanocyte proliferation and apoptosis. These miRNAs and regulatory processes further illuminate the pathogenesis of vitiligo and provide hope for the application of small molecules in the treatment of vitiligo. In this review, we summarize miRNA expression profiles in different tissues of vitiligo patients and the mechanisms by which key miRNAs mediate vitiligo development.

Keywords Vitiligo · microRNA · Melanocyte · Melanin · Polymorphism

Introduction

Vitiligo is a common pigment loss disease characterized by a significant decrease in melanocytes in the lesions [1, 2]. Depigmentation can occur on all parts of the body but is most commonly found on the back of the fingers, wrists, forearms, face, neck and around the genitals [3]. The theories of the pathogenesis of vitiligo are focused on autoimmunity, mental stress, oxidative stress, metabolic toxins and heredity [3–5]. However, the mechanism of melanocyte

destruction or apoptosis has yet to be fully elucidated. An increasing number of studies suggest that the occurrence and progression of vitiligo is caused by multiple factors and is polygenic, and noncoding RNAs may play a vital role in an individual's susceptibility to vitiligo [6].

Noncoding RNAs, including long non-coding RNA (lncRNA), microRNA (miRNA) and circular RNA (circRNA), play an important role in the regulation of gene expression. To our knowledge, there are still no studies on lncRNAs and circRNAs in the pathogenesis of vitiligo. In contrast, thus far, studies of noncoding RNA in the etiology of vitiligo have focused primarily on miRNAs.

miRNAs are a class of noncoding single-stranded RNA with a length of approximately 20–24 nucleotides [7]. During miRNA processing in the nucleus, primary miRNAs (pri-miRNAs) are first synthesized by RNA polymerase and then modified into precursor miRNAs (pre-miRNAs) by Drosha and its cofactor DGCR8. Pre-miRNAs are transported out of the nucleus through the Exportin-5/Ran-GTP complex and then cut by Dicer. miRNAs inhibit or degrade mRNA translation by binding to the 3'-UTR or 5'-UTR of the target mRNA at a posttranscriptional level [8–11]. Studies have shown that approximately 60% of human encoded

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protein genes are regulated by miRNAs [12] (Fig. 1). This review focuses on the expression profiles of miRNAs in different tissues of vitiligo patients and summarizes the latest knowledge of the molecular and cellular mechanisms of key miRNAs to pave the way for a new diagnosis and treatment for vitiligo.

miRNA expression profiles in vitiligo

miRNA differential expression profiles were obtained from skin lesion, melanocyte, peripheral blood mononuclear cells (PBMCs) and serum samples from patients with vitiligo [6, 13–15]. The results of the initial screen of the microarray, the PCR verification and the subsequent bioinformatics analysis provide an important basis for the in-depth study of the actions of miRNAs in the development of vitiligo (Table 1).

Skin miRNA expression profiles in vitiligo

Mansuri et al. found that there were 13 differentially expressed miRNAs in the lesion areas of nonsegmental vitiligo (NSV) when compared to the miRNAs in healthy controls. Among them, the expression levels of 12 miRNAs, including miRNA-1, miRNA-133b and miRNA-135a, in the skin lesions of NSV patients increased significantly, while

the expression level of miRNA-211 decreased. Bioinformatics analysis reveals that these miRNAs have a coordinated role of oxidative stress and autoimmunity in melanocyte destruction and disease development and are critical for the development or susceptibility of NSV [6].

Another study suggested that compared to the nonpathological regions of patients with vitiligo, lesions had 29 significantly upregulated miRNAs, of which 6 miRNAs were transfected into normal human epidermal keratinocytes (NHEK), and the quantitative proteomics results showed that a melanogenesis protein, tyrosinase related protein-1 (TRP1/TYRP1), was downregulated after 6 miRNAs were transfected. Under physiological conditions, melanocytes synthesize and transfer melanosomes to peripheral keratinocytes. Further evidence suggests that the above miRNAs may act in an integrated manner to regulate the process of melanosome transfer [16].

Serum miRNA expression profile in vitiligo

The expression of 20 miRNAs, including miRNA-146a and miRNA-191, in the sera of vitiligo mice was changed compared with that in the sera of control mice [17]. In another study from the same research group, the serum miRNA expression profiles of 10 patients with NSV and 20 healthy controls were examined; there were 31 differentially

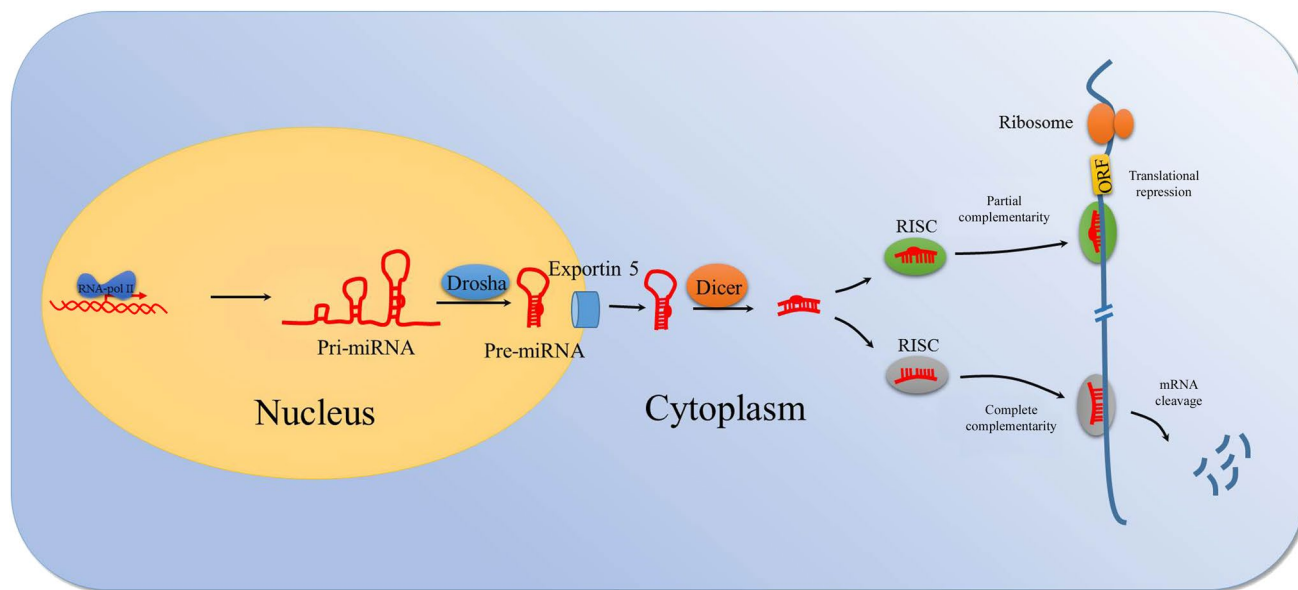


Fig. 1 Biogenesis of microRNA (miRNA). The initial miRNA transcript (pri-miRNA) is first processed by RNA polymerase III. Pri-miRNA has incomplete complementary double-stranded RNA regions and hairpin structures, which transformed into mature microRNA and underwent two consecutive splicing. In the nucleus, pri-miRNA is cut by Drosha enzyme to form the stem-loop structure of about 70 nt, that is, pre-miRNA. Pre-miRNA is then transported to the cytoplasm by the transporter Exportin-5 (Exp-5). Under the

action of Dicer enzyme, a single chain structure of miRNA with a length of 20–24 is produced, forming a mature miRNA. Mature microRNA then binds to the RNA-induced silencing complex (RISC), mediates the silencing of post-transcriptional gene expression via mRNA deadenylation followed by degradation (partial complementarity) or initiating mRNA cleavage activity (complete complementarity). pri-miRNAs, primary-miRNAs; pre-miRNAs, precursor miRNAs; RISC, The RNA-induced silencing complex

Table 1 microRNAs (miRNAs) expression profiles in vitiligo

Species	Sample	Up-regulated miRNAs		Down-regulated miRNAs		Refs.
		Count	List	Count	List	
Human	Peripheral blood	2	miR-202-3p, miR-5194	32	let-7b-3p, let-7f-1-3p, miR-1228-3p, miR-1234-3p, miR-1238-3p, miR-1249-3p, miR-1281, miR-191-3p, miR-423-5p, miR-4433a-5p, miR-4649-3p, miR-4655-3p, miR-4665-3p, miR-4698, miR-4701-5p, miR-4745-5p, miR-5703, miR-6069, miR-630, miR-6507-3p, miR-6508-5p, miR-6515-3p, miR-6737-3p, miR-6785-3p, miR-6797-3p, miR-6800-3p, miR-6819-3p, miR-6865-3p, miR-6870-3p, miR-6889-3p, miR-762, miR-766-3p	Shang et al. (2017) [15]
Mouse	Serum	9	miR-146a, miR-182, miR-494, miR-342-3p, miR-339-3p, miR-191, miR-685, miR-210, miR-188	11	miR-345, miR-93, miR-26a, miR-20a, miR-375, miR-340, miR-26b, miR-99b, miR-652, miR-451, let-7c	Shi et al. (2014) [17]
Human	Serum	24	let-7b, miR-16, miR-451, miR-25, miR-15b, miR-1323, miR-186*, let-7a, miR-19b, miR-636, miR-885-3p, let-7c, miR-107, let-7i, let-7 g, miR-550, miR-223, miR-486-5p, let-7d*, miR-627, miR-548c-5p, miR-15a, miR-190, miR-146a	24	miR-1914*, miR-187*, miR-1305, miR-516a-5p, miR-557, miR-574-5p, miR-663, miR-1182, miR-139-3p, ebv-miR-BART7, miR-1181, miR-1225-5p, miR-623, miR-1202, miR-149*, miR-320a, miR-1307, miR-610, miR-877, miR-32*, miR-1226*, miR-1225-3p, miR-1207-5p, hcmv-miR-UL70-3p	Shi et al. (2016) [33]
Human	Skin	5	miR-99b, miR-155, miR-199a-3p, miR-125b, miR-146b	1	miR-145	Šahmatova et al. (2016) [25]
Human	Serum	17	miR-16, miR-451, miR-223, miR-19b, miR-151-5p, miR-25, miR-186, miR-195, miR-590-5p, miR-19a, miR-30d, miR-192, miR-222, miR-93, miR-146a, miR-29a, miR-191	13	miR-1274a, miR-574-3p, miR-1290, miR-720, miR-10a, miR-483-5p, miR-125b, miR-150, miR-139-5p, miR-26a, let-7d, miR-30b, miR-30c, miR-126	Shi et al. (2013) [18]
Human	Skin (case/control)	12	miR-1, miR-133b, miR135a, miR-183, miR-190, miR-214, miR-301b, miR-30a-3p, miR-375, miR-487a, miR-517c, miR-616	1	miR-211	Mansuri et al. (2014) [6]
Human	Skin (nonleison of case/control)	28	let-7c, miR-100, miR-10a, miR-1180, miR-135a, miR-135b, miR-136, miR-145, miR-183, miR-184, miR-194, miR-25, miR-296, miR-30a-3p, miR-30a-5p, miR-30b, miR-30e-3p, miR-328, miR-34b, miR-383, miR-487a, miR-548d-5p, miR-577, miR-581, miR-642, miR-654-3p, miR-9, miR-99b	1	miR-141	Mansuri et al. (2014) [6]
Human	Skin (leison/nonleison of case)	3	miR-136, miR-296, miR-328	0	–	Mansuri et al. (2014) [6]

Table 1 (continued)

Species	Sample	Up-regulated miRNAs		Down-regulated miRNAs		Refs.
		Count	List	Count	List	
Human	Skin (case/control)	29	miR-423, miR-185, miR-326, miR-202, miR-518 C*, miR-518b, miR-324-5p, miR-525, miR-373*, miR-498, miR-302c*, miR-129, miR-198, miR-527, miR-320, miR-526c, miR-450, miR-503, miR-let-7e, miR-383, miR-516-5p, miR-335, miR-206, miR-519e, miR-526a, miR-518a-2*, miR-184, miR-500, miR-452	-	NO DATA	Vaish et al. (2019) [16]
Human	PBMC	2	miR-224-3p, miR-4712-3p	1	miR-3940-5p	Wang et al. (2015) [13]
Human	PIG1	7	miR-181a, miR-31, miR-185, miR-320b, miR-423-5p, miR-103, miR-93	3	miR-1826, let-7c, miR-125b	Zhang (2011) [21]
Human	PIG3V	3	miR-423-5p, miR-320b, miR-93	5	miR-138, miR-455-3p, miR-18a, miR-362-5p, miR-130b	Zhang (2011) [21]

Asterisk represents that a mature microRNA is expressed from both the 5'-arm and the 3'-arm

expressed miRNAs, of which 12 miRNAs had a fold-change of more than 3.0 times. Three of the miRNAs (miRNA-16, miRNA-19b and miRNA-720) seemed to be the best serum markers to differentiate NSV patients from healthy controls [18].

In one study of a Chinese population, 29 upregulated and 71 downregulated miRNAs were screened. GO analysis was used to assess the function of differentially expressed miRNA-associated predicted target genes, suggesting that the functions of the most significantly enriched target gene are focused on axon guidance, cell adhesion and cell junctions [15].

PBMC miRNA expression profile in vitiligo

miRNA microarray analysis was used to compare the miRNA expression profiles of PBMCs in the peripheral blood of patients with NSV and those of normal controls. Four miRNAs in the PBMCs of NSV patients showed significant differential expression, and the results showed that miRNA-224-3p, miRNA-2682-3p and miRNA-4712-3p expression was upregulated, and miRNA-3940-5p expression was significantly downregulated. The abovementioned miRNAs were further verified by PCR after the sample was added. The results showed that the expression of miRNA-224-3p and miRNA-4712-3p was upregulated in the PBMCs of NSV patients, and the expression of miRNA-3940-5p was downregulated, and these results are consistent with the results of the miRNA microarray data analysis. This study suggests that miRNAs may regulate T lymphocyte-mediated immune imbalance in vitiligo and that targeting these miRNAs may be a potential treatment for vitiligo [13].

Melanocyte miRNA expression profile in vitiligo

Hydrogen peroxide (H₂O₂) can induce oxidative stress in melanocytes and stimulate the pathological process of melanocyte injury in vitiligo [19, 20]. By differential analysis of the miRNA microarray expression profile, Zhang et al. found that 10 miRNAs in PIG1 melanocytes (a strain of normal human skin melanocytes) changed after H₂O₂ treatment, and 7 miRNAs were upregulated and 3 were downregulated. In PIG3V melanocytes, an immortalized melanocyte cell line from vitiligo patients, three miRNAs were upregulated and 5 were downregulated when treated with H₂O₂. Interestingly, after H₂O₂ treatment, three miRNAs (miRNA-93, miRNA-320b and miRNA-423-5p) were altered in both melanocyte types. These three miRNAs were further verified by RT-PCR. The trend between the miRNA microarray and PCR is consistent. The expression of miRNA-93 and miRNA-320b in PIG1 melanocytes decreased after H₂O₂ treatment. The expression of miRNA-423-5p in the two kinds of melanocytes was higher after H₂O₂ treatment than before treatment,

and the expression level of PIG3V cells was significantly different before and after treatment. The results were consistent with the microarray results [21].

Pivotal miRNAs

miRNA-155-5p

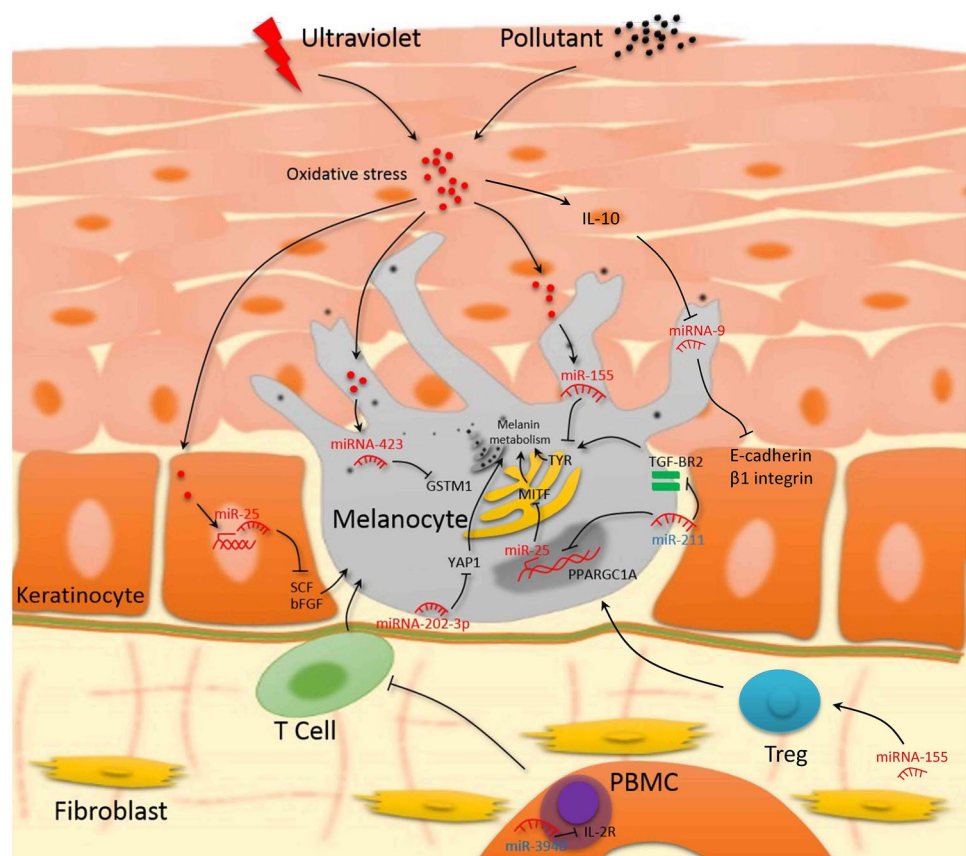
miRNA-155-5p (miRNA-155) is considered to be a common oncogenic miRNA involved in many biological processes, such as hematopoietic cell differentiation, immune cell differentiation, inflammatory and immune response, muscle development and adipose differentiation [22–24]. In situ hybridization analysis showed that miRNA-155 expression increased in the epidermis of patients with vitiligo. In human primary melanocytes and keratinocytes, vitiligo-related cytokines induced the production of miRNA-155, and miRNA-155 inhibited the expression of melanogenesis-related genes and changed the expression of IFN-regulated genes in melanocytes and keratinocytes. It is suggested that miRNA-155 is involved in the pathogenesis of vitiligo [25] (Fig. 2). Interestingly, miRNA-155 was found to be down-regulated in T cells from patients with vitiligo. Further research found that miRNA-155 agonists significantly

reduced the growth rate of CD8⁺ T cells and promoted the proliferation of melanocytes by inducing an increase in the percentage of Treg cells. In contrast, miRNA-155 antagonists inhibited melanocyte proliferation by reducing the percentage of Treg cells. In short, miRNA-155 protects melanocyte survival by increasing the number of Treg cells and reducing the number of CD8⁺ T cells, which may provide new prospects for the treatment of vitiligo [26].

miRNA-211-5p

miRNA-211 positively regulates pigment production by targeting transforming growth factor beta receptor 2 (TGFBR-2). TGFBR-2 is considered to be a negative regulator of tyrosinase (TYR) and TYRP-1 [27]. Therefore, miRNA-211 plays an important role in the regulation of melanocyte biology and development. One study found that miRNA-211 acts as a metabolic switch in nonpigmented melanoma cells [28]. Another study confirmed one aspect of the above conclusion. This microarray study found that the expression of miRNA-211 was significantly decreased in the lesions of vitiligo and in the vitiligo cell line PIG3V. Of all the predicted miRNA-211 targets, analysis revealed an inverse upregulation of peroxisome proliferative activated receptor, gamma, coactivator 1

Fig. 2 Multiple miRNAs are involved in vitiligo. miRNA-155 is involved in abnormal melanin metabolism. miRNA-211, miRNA-25 and miRNA-423 regulate oxidative stress during melanocyte injury. SCF, supercoiling factor; bFGF, fibroblast growth factor 2; YAP1, Yes associated protein 1; IL-2R, interleukin 2 receptor; PPARGC1A, PPARG coactivator 1 alpha; GSTM1, Glutathione S-transferase Mu 1; TYR, tyrosinase; MITF, melanogenesis associated transcription factor; TGF-BR2, transforming growth factor beta receptor 2



alpha (PPARGC1A), ribonucleotide reductase regulatory subunit M2 (RRM2) and TAO kinase 1 (TAOK1), which was confirmed with RNA-seq and gene expression array data derived from biopsy samples taken from patients with vitiligo (GEO accession series GSE53148) [29]. In vitro, it was further found that miRNA-211 can bind to the 3'-UTR site of PPARGC1A/PGC1- α and inhibit its expression. The increased production of reactive oxygen species in vitiligo cells may be partly due to the abnormal expression of miRNA-211 and its subsequent regulation of its target gene. miRNA-211 coated with nanoparticles can improve the oxygen consumption rate of PIG3V cells to a certain extent, so miRNA-211 and its target genes may be potential biomarkers and therapeutic targets for vitiligo [30–32].

miRNA-25-5p

The serum level of miRNA-25 in patients with vitiligo was increased, and this serum level was related to the activity of vitiligo. The reason may be that oxidative stress can upregulate the level of miRNA-25 in melanocytes and keratinocytes by inducing demethylation of the miRNA-25 promoter region. Similarly, the recovery of miRNA-25 promoted H₂O₂-induced damage to melanocytes and resulted in melanocyte dysfunction. In this process, MITF, a target gene of miRNA-25, is involved in the damage to melanocytes. Further experiments have shown that miRNA-25 can inhibit the production and secretion of stem cell factor (SCF) and basic fibroblast growth factor (bFGF) by keratinocytes and thus inhibit the paracrine protection of melanocytes under oxidative stress [33]. Therefore, it is worthwhile to study the possibility of miRNA-25 as a target of antioxidation therapy for vitiligo.

miRNA-423-5p

The expression of miRNA-423 in the immortalized human epidermal melanocytes PIG1 and the vitiligo melanocytes PIG3V was upregulated after H₂O₂ treatment. Therefore, miRNA-423 may be involved in the oxidative stress response of melanocytes [21]. This study further revealed that miRNA-423 can decrease the viability of human melanocytes and promote melanocyte apoptosis under the oxidative stress induced by H₂O₂. It was proven that miRNA-423 may be a risk factor for regulating oxidative stress damage in human melanocytes. Further studies showed that miRNA-423 mediated oxidative stress injury in human melanocytes by targeting GSTM1, which is a key antioxidant component of human melanocytes, and has significant antioxidant capacity [21, 34].

miRNA-202-3p

miRNA-202-3p may participate in the occurrence and development of vitiligo. Overexpression of miRNA-202-3p can significantly inhibit the proliferation and adhesion of human melanocytes, inhibit melanin synthesis and promote apoptosis. Silencing miRNA-202-3p can promote melanin synthesis but has no obvious effect on cell proliferation, adhesion and apoptosis. Yes1 associated transcriptional regulator (YAP1) may be a direct target gene of miRNA-202-3p, and it affects the expression of p73 and BCL2 binding component 3 (PUMA) in cell proliferation and apoptosis and affects the biological function of normal melanocytes [14].

miRNA-3940-5p

Vitiligo is an immune disorder characterized by the presence of activated T lymphocytes in the skin and the destruction of melanocytes, which is one of the main mechanisms of the pathogenesis of NSV [35–37]. The expression of miRNA-3940 in the PBMCs of patients with NSV was found to be downregulated. Following the construction of the miRNA-3940-inhibited T lymphoblastic leukemia cell line HuT78, interleukin 2 receptor γ (IL-2R γ), an immune-associated gene of vitiligo, has been confirmed to be the target gene of miRNA-3940. After miRNA-3940 was inhibited, the proliferation rate of HuT78 cells was significantly upregulated. Based on these results, miRNA-3940 may be a novel miRNA that plays a potential role in the mechanism of immune imbalance in vitiligo [38].

miRNA-9-5p

The skin microenvironment is critical to normal melanocyte function [39]. Human vitiligo lesions showed a decrease in adhesion molecules, such as E-cadherin and β 1 integrin [36, 40, 41]. Therefore, the reduction in the adhesion of melanocytes to the adjacent keratinocytes and the loss of melanocytes from the epidermis are key steps in the pathogenesis of vitiligo [42]. The melanocytes adhere and migrate to the edge regions to initiate the repigmentation process [43]. miRNA-9 is involved in the adhesion and migration of melanocytes during UVB-induced vitiligo repigmentation [35]. In this process, Su M et al found that UVB could increase the level of IL-10 in HaCaT cells and trigger the methyl modifications of miRNA-9 induced by the methyltransferase DNMT3A, thereby reducing the level of miRNA-9. It was suggested that miRNA-9 targeted and inhibited E-cadherin and β 1 integrin in HaCaT cells and inhibited PIG1 cell migration when HaCaT cells were exposed to UVB. Therefore, once miRNA-9 is inhibited, the migration of PIG1 cells

to HaCaT cells can be improved. To be more optimistic, interfering with miRNA-9 may provide an opportunity to treat vitiligo.

miRNA polymorphism

Single nucleotide polymorphism (SNP) is the most common gene variation in human genes and can affect gene expression, transcription and modification [44, 45]. It is one of the important reasons for disease susceptibility, and individual and ethnic differences in drug reactivity. Studies have shown that SNPs of miRNAs are associated with many human diseases, which can affect the phenotype or development of the disease [46–48].

Four SNP loci of miRNAs, including miRNA-146a rs2910164, miRNA-149 rs2292832, miRNA-196a2 rs11614913, and miRNA-499 rs3746444, were identified from 400 known human pre-miRNAs in patients with vitiligo and controls. It was found that only individuals with the miRNA-196a2 CC genotype had lower susceptibility to vitiligo than patients with the combined genotype of TT and TC. The genotypes of miRNA-196a2 rs11614913 CC combined with TT and TC were further analyzed by stratification [49]. A subsequent study showed that rs11614913 T>C can reduce the early apoptosis rate of melanocytes and has a protective effect against melanocyte apoptosis under the oxidative stress induced by H₂O₂. TRP-1 was proven to be the target gene of miRNA-196a2 [50].

Further study evaluated the potential association between the rs11614913 SNP in miRNA-196a2 and the serum tyrosine (Tyr) levels in 116 patients with vitiligo and 116 controls. Interestingly, individuals with a TT+TC genotype in miRNA-196a2 and high serum Tyr levels had a higher risk of vitiligo than patients with lower CC genotypes and low Tyr levels. In addition, the rs11614913 C allele enhanced its inhibitory effect on Tyr expression, and its downregulation in melanocytes successfully reduced intracellular ROS levels and apoptotic rates [51]. In summary, it suggested that miRNA-196a2 polymorphisms can regulate Tyr levels and thus affect susceptibility to vitiligo.

Conclusion

The differential expression of miRNAs that have been reported provides an opportunity for us to understand the pathogenesis of vitiligo. Regulating miRNA and its downstream signaling pathway may provide more potentially valuable options for the prevention and treatment of vitiligo.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors.

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