

Update on the role of noncoding RNAs in vitiligo

Ting Zhou, Dong Li, Yunhua Deng

Department of Dermatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China.

Vitiligo is a prevailing disfiguring skin disorder characterized by the selective absence of functional melanocytes, affecting 0.5% to 1% of the global population.^[1] Several hypotheses have been proposed for its pathogenesis, including autoimmunity, oxidative stress, genetic and environmental factors, and metabolic abnormalities.^[2] No individual factor can completely explain the complex progression of this disease. Most of the human genome encodes RNAs that are not translated into proteins, termed noncoding RNAs (ncRNAs).^[3] Accumulating studies have demonstrated that ncRNAs act as regulators of vitiligo. We summarize the regulation of ncRNAs in the pathogenesis of vitiligo, especially microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs, to pave the way to develop more effective diagnostic and therapeutic approaches for vitiligo [Figure 1].

MiRNAs are short ncRNAs approximately 22 nucleotides in length that combine with the RNA-induced silencing complex (RISC). Then, the RISC acts on its target by repressing transcription or cleaving mRNA. In vitiligo, differential expression profiles of miRNAs have been reported by several studies. The specimens came from different sources, such as lesions,^[4] peripheral blood mononuclear cells (PBMCs),^[5] serum,^[6] and exosomes from keratinocytes.^[7] With the identification of differentially expressed miRNAs, accumulating research has been carried out to determine the role of miRNAs in the regulation of oxidative stress, autoimmunity, and melanocyte biology in vitiligo.

The oxidative stress theory is the main hypothesis for the pathogenesis of vitiligo. Many studies have confirmed a bias between the pro-oxidant and antioxidant systems in vitiligo, supporting its pathogenic role.^[8] MiR-211 expression was downregulated in PIG3V (a vitiligo cell line) and skin specimens from vitiligo; in contrast, expression of its target PPARγ coactivator 1 alpha (PGC1A) was upregulated.^[9] After analysis of oxygen consumption rates (OCRs), inherent respiratory defects in PIG3V cells were found.

Interestingly, the restoration of miR-211 could partly reverse the OCRs. In addition, elevated reactive oxygen species (ROS) levels in PIG3V cells were returned to baseline by knockdown of PGC1A. Moreover, ROSs impair cellular redox potential in the endoplasmic reticulum (ER), giving rise to the accretion of harmful misfolded proteins, which induce the unfolded protein response. Sun *et al*^[10] confirmed that the expression of miR-421 was increased and that of receptor-interacting serine/threonine kinase 1 (RIPK1) was downregulated in an ER stress model of human melanocytes. However, knockdown of miR-421 diminished ER stress-related apoptosis mediators and activated the PBK/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) signaling pathway, and the effects were reversed by RIPK1-shRNA. The PBK/AKT/mTOR signaling pathway is known to be associated with cell survival. These findings indicated that melanocytes could survive ER stress-induced cell damage by knocking down miR-421, indicating the potential of miR-421 as a therapeutic target.

Vitiligo has been clearly identified as an autoimmunity-related disease. It was observed that miR-155 expression in T cells of individuals with vitiligo was downregulated.^[11] Then, a remarkable reduction in the number and function of regulatory T cells (Tregs) and an increase in CD8+ T cells were found after knocking down miR-155. Another study validated that miR-21-5p expression in PBMCs was downregulated, whereas the expression of signal transducer and activator of transcription 3 (STAT3) was elevated in vitiligo.^[12] Further study observed that overexpression of miR-21-5p induced an increase in the Treg/effector T cell (Teff cell) proportion by targeting STAT3. Wang *et al*^[13] found that miR-3940-5p expression was downregulated in the PBMCs of individuals with non-segmental vitiligo. Subsequently, increases in T-cell numbers and interleukin 2 receptor subunit gamma (IL-2RG) levels were verified in the HuT78-miR-3940-5p-inhibited cell line, suggesting that the miR-3940-5p-IL-2RG axis might affect T-cell proliferation, hence facilitating vitiligo development.

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Correspondence to: Yunhua Deng, Department of Dermatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, Hubei 430030, China
E-Mail: 820331158@qq.com

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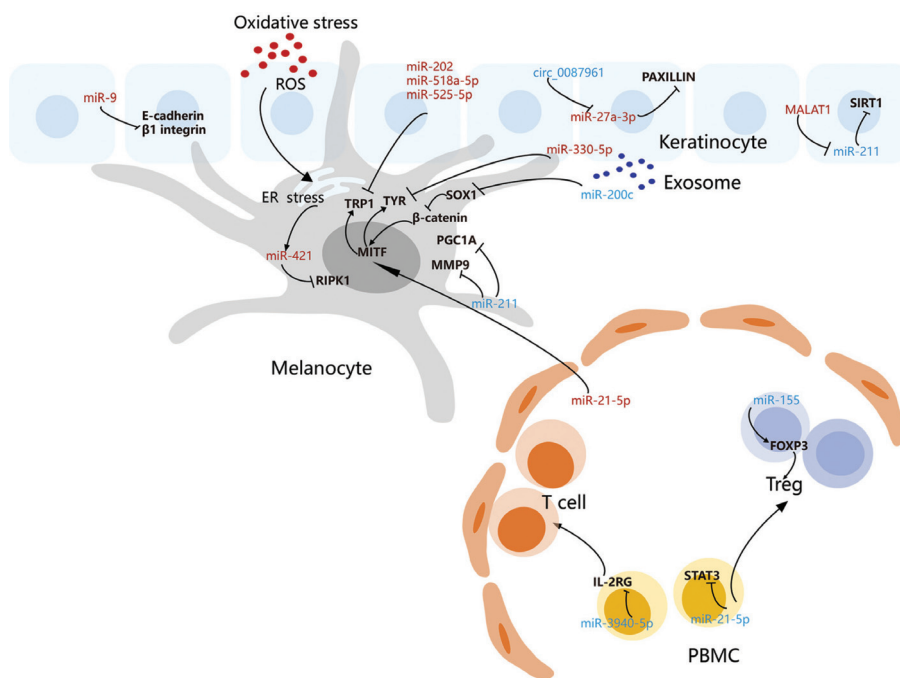


Figure 1: Regulation of multiple ncRNAs in vitiligo. Red miRNAs represent the upregulated ones; blue miRNAs represent the downregulated ones. ER: Endoplasmic reticulum; FOXP3: Forkhead box P3; IL-2RG: Interleukin 2 receptor subunit gamma; miRNA: microRNA; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; MMP9: Matrix metalloproteinase 9; MITF: Microphthalmia-associated transcription factor; ncRNAs: Noncoding RNAs; PBMC: Peripheral blood mononuclear cells; PGC1A: PPARG coactivator 1 alpha; ROS: Reactive oxygen species; RIPK1: Receptor-interacting serine/threonine kinase 1; SOX10: SRY (sex-determining region Y)-box 10; SIRT1: Sirtuin 1; STAT3: Signal transducer and activator of transcription 3; SOX1: SRY (sex-determining region Y)-box 1; TRP1: Tyrosinase-related protein 1; TYR: Tyrosinase; Treg: Regulatory T cells.

It is well established that dysregulated melanocyte biology by genetic and nongenetic factors ultimately contributes to depigmentation in vitiligo. MiR-21-5p expression in patients with vitiligo was found to be higher than that in controls.^[14] An *ex vivo* study observed that miR-21-5p overexpression in melanocytes contributed to a significant reduction in SRY (sex-determining region Y)-box 5 (SOX5), β-catenin, and cyclin-dependent kinase 2 expression and an increase in microphthalmia-associated transcription factor expression. This finding indicated that miR-21-5p might serve as a compensatory mechanism for melanocytes, although this was insufficient to counterbalance other detrimental mechanisms. TYR and TRP1 play a critical role in the control of melanin production. After transfection of six miRNAs (miR-185, miR-202, miR-525-5p, miR-326, miR-518a-5p, and miR-518c) that showed significantly upregulated expression in lesions compared with the nonlesional epidermis of vitiligo, TRP1 expression was inversely downregulated in normal human epidermal keratinocytes.^[4] In accordance with previous results, a recent study demonstrated that the TT genotype of miR-196a-2 was the most prevalent genotype in vitiligo patients. It was suggested that miR-196a-2 polymorphisms might alter TYR expression, which not only affects patients' susceptibility to vitiligo but also impacts their therapeutic response.^[15] Zhao *et al*^[7] analyzed the miRNA profile of exosomes secreted by keratinocytes from vitiligo lesions (VLKs) and noticed a remarkable decrease in miR-200c levels and relatively higher SOX1 expression in melanocytes cocultured with exosomes secreted by VLKs. SOX1 was proven to downregulate β-catenin expression, thereby suppressing

melanogenesis-related genes. Liu *et al*^[16] found that exosomes secreted from keratinocytes that overexpressed miR-330-5p induced a significant decrease in the production of melanin and the expression of TYR in melanocytes. Thus, these elegant studies further illustrated the interesting crosstalk between keratinocytes and melanocytes. Another study focused on melanocyte migration and disclosed the role of the p53-transient receptor potential cation channel subfamily M member 1/miR-211-matrix metalloproteinase 9 axis, whose activation might improve repigmentation outcomes in vitiligo patients.^[17] E-cadherin and β1 integrin are major adhesion molecules that mediate melanocyte-keratinocyte adhesion and melanocyte-extra-cellular matrix adhesion, respectively. Skin lesion specimens of individuals with vitiligo revealed that miR-9 levels were elevated but E-cadherin and β1 integrin levels were reduced. However, ultraviolet B (UVB) treatment in HaCaT keratinocytes reversed this state, thereby recovering the adhesion function of HaCaT cells and facilitating PIG1 cell migration to HaCaT cells.^[18]

LncRNAs are defined as a group of ncRNAs whose length exceeds 200 nucleotides. In recent years, research on vitiligo and lncRNAs has emerged. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), a long noncoding RNA, was identified as an 8000 nucleotide-long transcript. To date, three major functions have been attributed to MALAT1: mRNA splicing regulation, transcriptional regulation, and competitive endogenous RNA function.^[19] An increase in MALAT1 and an accompanying decrease in miR-211 were found recently in VLKs. MALAT1 could specifically bind to miR-211 and

suppress its expression, resulting in an increase in sirtuin 1 (SIRT1), which is a target of miR-211.^[20] SIRT1 was suggested to increase the level of differentiated keratinocytes and protect them from UVB-induced DNA damage, which may explain the intriguing fact that patients with skin cancer are insusceptible to vitiligo. Taurine-upregulated gene 1 (TUG1) expression was obviously decreased in patients with vitiligo. Moreover, the researchers reported an intriguing finding that TUG1 levels were positively related to the time of appearance of the last lesion in individuals with vitiligo, indicating the relationship between lncRNA TUG1 and vitiligo activity.^[21] In addition, an independent genetic association study verified that the association of vitiligo with plasmacytoma variant translocation 1 (PVT1) SNP rs10087240 was highly significant, thus confirming that PVT1 was a vitiligo susceptibility locus in the European population.^[22]

CircRNA, another unique type of ncRNA, is characterized by a distinctive closed-loop structure.^[3] In a recent study, Li *et al.*^[23] identified circRNA-miRNA-mRNA regulatory networks that might have a crucial role in the pathology of vitiligo. Their analyses showed that circ_0087961-miR-27a-3p-PAXILLIN might be a promising axis related to vitiligo. Paxillin, a 69-kDa adapter protein, promotes the adhesion ability of melanocytes. This research lays a theoretical foundation for further investigation of circRNA-miRNA-mRNA regulatory networks.

To date, research on the regulation of ncRNAs in vitiligo is still in the developmental stage, especially for lncRNAs and circular RNAs. However, accumulating evidence has validated the potential of ncRNAs in the regulation of oxidative stress, autoimmunity, and melanocyte biology in vitiligo. Research on miRNAs derived from exosomes is gradually showing their roles in unique intercellular communication. As theoretical studies increase, more options will be available for the diagnosis and treatment of vitiligo in the future.

Conflicts of interest

None.

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