

The Functional Mechanism of MicroRNA in Oral Lichen Planus

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Abstract: Non-coding RNAs (ncRNAs) are transcribed from the genomes of mammals and other complex organisms, and many of them are alternately spliced and processed into smaller products. Types of ncRNAs include microRNAs (miRNAs), circular RNAs, and long ncRNAs. miRNAs are about 21 nucleotides long and form a broad class of post-transcriptional regulators of gene expression that affect numerous developmental and physiological processes in eukaryotes. They usually act as negative regulators of mRNA expression through complementary binding sequences in the 3'-UTR of the target mRNA, leading to translation inhibition and target degradation. In recent years, the importance of ncRNA in oral lichen planus (OLP), particularly miRNA, has attracted extensive attention. However, the biological functions of miRNAs and their mechanisms in OLP are still unclear. In this review, we discuss the role and function of miRNAs in OLP, and we also describe their potential functional roles as biomarkers for the diagnosis of OLP. MiRNAs are promising new therapeutic targets, but more work is needed to understand their biological functions.

Keywords: oral lichen planus, miRNA, biomarker, therapy

Introduction

Oral lichen planus (OLP) is a chronic disease that mainly affects the immune system,¹ involving the oral mucosa, that features recurrence and remission.^{2,3} In the general population, the prevalence of OLP ranges from 0.5% to 4%, and it can appear 4–5 years after birth. In clinical practice, six clinical subgroups of OLP can be seen, singly or in combination: plaque-like, reticular, papular, erosive/ulcerative, atrophic, and bullous. The reticular, erosive/ulcerative, and plaque-like subtypes are the most common.^{4–6} In the literature, papular, plaque-like, and reticular OLP lesions are called non-erosive OLP (NEOLP) lesions, while atrophic/erosive, bullous, and ulcerative types are referred to as erosive OLP (EOLP).⁷ Because 1.63% of OLP lesions progress to oral squamous cell carcinomas (OSCC), the World Health Organization designated OLP as a potentially malignant oral condition in 2005.^{8–10} Thus, it is important to better understand the mechanisms of and treatments for OLP; in addition, the role of non-coding RNAs (ncRNAs) in OLP has attracted increasing attention.

NcRNAs are the most abundant cellular RNAs in all organisms.¹¹ In contrast to mRNAs, ncRNAs, either on their own or in complex with proteins, have important cellular functions and are not translated into proteins.¹² NcRNAs are necessary modulators of 90 types of gene expression and perform a signal-transduction role in cells.¹³ MicroRNAs (miRNAs), a type of ncRNA, are small and endogenous RNAs that regulate gene expression.¹⁴ They play an essential role in cancer; identifying the role of miRNAs in OLP as a pre-cancer disease is essential. MiR-123, miR-647, and miR-31 may, through circ_003912, have a role in the pathogenesis of EOLP.¹⁵ The apoptosis of keratinocytes may be promoted by miR-122 in OLP.¹⁶ Further, changes in the expression of miR-21 and miR-125a may lead to malignant transformation.¹⁷ In addition, a number of miRNAs show altered expression in OLP. Therefore, due to its involvement in the pathogenesis of OLP, the role of miRNA as a diagnostic and prognostic biomarker should also not be ignored.

We conducted searches on the PubMed database regarding OLP and miRNA, with the search terms “oral lichen planus”, “OLP”, “oral lichenoid disease”, “OLD”, “miRNA”, “microRNA”, and others. The Boolean operators “AND” and “OR” were used to combine different search terms. Our selection criterion was that the result must be verified in fresh tissue, embedded sample tissue, or human body fluid. Our search identified that, although some previous work has summarized the role of miRNA in OLP, the scopes of the searches have been too broad, and the mechanisms not sufficiently elaborated, so in this study, we identified miRNAs reported in several search results and elaborated the mechanisms of their roles in OLP.

The study of miRNAs is vital to understanding OLP. Therefore, in this review, we examine the role that miRNAs play in OLP and summarize their mechanisms and functions of miRNAs and future directions in therapeutic research.

Overview of Oral Lichen Planus

OLP is a chronic inflammatory disease that affects the oral mucosa and has distinct relapses and remissions. Typically, it affects the tongue, buccal mucosa, and gingiva. Oral lesions are always symmetrical on both sides, and a patient can have two or more forms of OLP simultaneously.⁴

Forms of OLP have also been reported that have a relationship with metabolic syndrome (MS) in addition to its usual symptoms. MS in OLP patients is higher than in controls. During treatment observation, metabolic complications should be considered. In addition, body mass index and triglyceride levels are also higher in OLP patients, and the levels of inflammatory cytokines may be increased by lipids, then occur or affect OLP. In addition, glucose tolerance and blood pressure are higher in OLP patients. The relationship between OLP and MS should not be ignored.¹⁸

The rate of malignant transformation of OLP is between 0% and 10%. A recent meta-analysis found that 1.1% of OLP lesions convert into OSCC, with a higher frequency among alcoholics, smokers, and people infected with hepatitis C. Invasive OLP appears to have the highest frequency of progression to OSCC. The most common malignant transformations occur in lesions confined to the tongue. OLP lesions were found to develop into OSCC lesions after an average of 5.5 years. In addition, compared to individuals with original OSCC, OSCC patients with previous OLP lesions had a greater probability of tumor recurrence.¹⁹

Several factors are associated with the etiology of OLP, including stress, genetic background, the stimulation of dental materials, reaction to drugs, autoimmunity, and other factors. Depression and quality of life are also closely related to the development of OLP.²⁰ Additionally, COVID-19 vaccination may also induce OLP.²¹

Much controversy remains regarding the pathogenesis of OLP, but immune dysregulation is the most likely cause.^{22,23} Cytokines play a vital role in the initiation and maintenance of immune response and inflammatory and intercellular cross-talk, and cytokines are soluble proteins.²⁴ Tumor necrosis factor-alpha (TNF- α), interferon (IFN)-C, and keratinocyte/T cell/antigen cell connections are thought to be generated by cell-mediated immunity induced by endogenous or external stimuli in OLP.^{1,2,25} A recent study found that the expression of interleukin-27 (IL-27) in severe OLP was significantly higher than in a control group, and IL-27 was positively correlated with abnormal epithelial cell proliferation, suggesting that IL-27 may have a relationship with the development of OLP.²⁶ In the peripheral blood, IL-12 and IL-1 β may affect innate lymphoid cells (ILCs), which could lead to immune dysregulation and influence the OLP.²⁷ Inflammation-related disorders exhibit a strong link between miRNAs and cytokines. Because many miRNAs are involved in OLP with different expression levels, research on their roles in the pathogenesis of OLP is essential.²⁸

Overview of miRNAs

MiRNAs are ncRNAs with a length of 20–25 nucleotides that influence gene expression after transcription.²⁹ The majority of mature miRNA sequences are found in ncRNA introns, ncRNA exons, and pre-mRNA introns, and miRNAs are processed from protein-coding gene introns or RNA polymerase II-specific transcripts of separate genes.^{30,31} Increasing evidence demonstrates that miRNAs act as key regulators of development and cellular homeostasis by controlling a variety of biological processes. For regulatory functions, miRNAs assemble into an RNA-induced silencing complex (RISC) to activate the complex to target mRNA. MiRNAs bind to the 3' untranslated region (3'UTR) of target mRNA and play a regulatory role in post-transcriptional control. Partial base pairing causes translation inhibition and functional protein degradation, while full or near-perfect complementary base pairing causes mRNA breakdown (Figure 1).

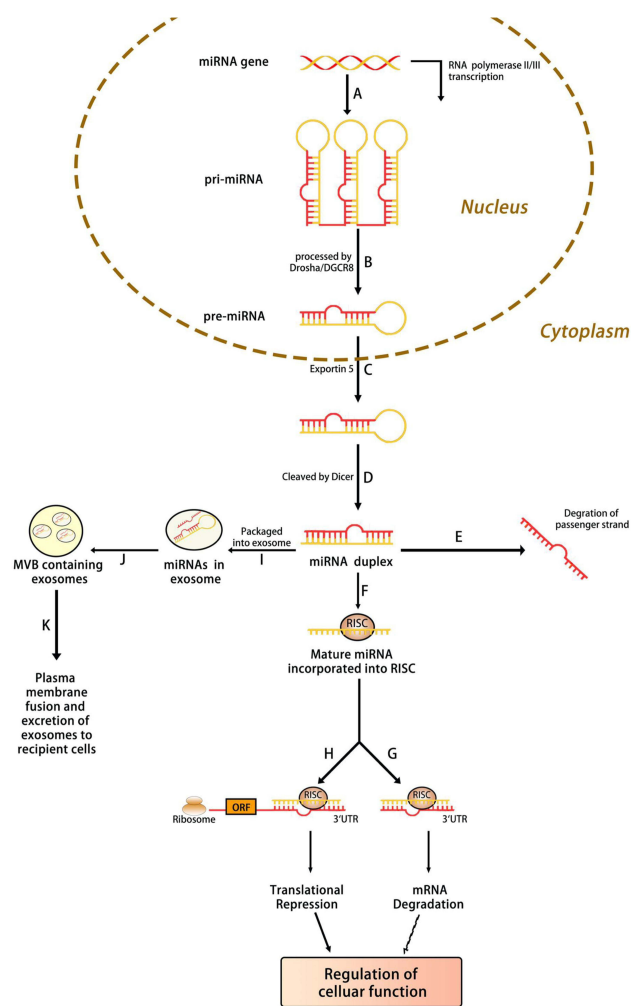


Figure 1 Biogenesis of microRNA. **(A)** MiRNA is transcribed by RNA polymerase (Pol) II or III into primary (pri)-miRNA, which is then **(B)** processed by Drosha into precursor (pre)-miRNA. **(C)** The pre-miRNA is transported from the nucleus into the cytoplasm by exportin 5, where it is then **(D)** processed by Dicer into a miRNA duplex. **(E)** The unwinding of the duplex results in the degradation of the passenger strand, and the **(F)** incorporation of the mature strand into RNA-induced silencing complex (RISC). The RISC then suppresses the gene expression of a target messenger RNA (mRNA) by either **(G)** mRNA degradation or **(H)** translational repression, resulting in the regulation of the cellular function. **(I)** Furthermore, miRNAs can also be packaged into exosomes, which are then **(J)** compartmentalized into a multivesicular body (MVB). **(K)** The MVB fuses with the plasma membrane, resulting in the transfer of miRNA-containing exosomes to recipient cells and mediating intercellular gene regulation.

MiRNAs are implicated in various physiological and pathological processes, including critical roles in inflammation and the immune response.³² Moreover, a range of biological functions are associated with miRNAs, including organogenesis, cell differentiation, metabolism, and apoptosis; miRNAs also have an essential role in intercellular communication.³⁰ Accumulating evidence demonstrates that human diseases such as cancer, neurological disorders, cardiovascular disease, and autoimmune illnesses are related to abnormal cellular levels of certain miRNAs.³³ For example, the expression of miRNAs is different in some cancer tissues. Downregulated miRNAs can increase the expression of oncomirs, while upregulated miRNAs may lead to the suppression of tumor suppressor genes. Therefore miRNAs may play a role in the actions of both tumor suppressors and oncogenes.³⁴

The levels of miRNAs in patients are different from those in healthy individuals. In a Canadian population, several miRNAs showed differential expression levels from those in healthy individuals; specifically, 15 miRNAs were increased, and 7 miRNAs were reduced.³⁵ Therefore, miRNAs can be thought of as biomarkers of disease activity. To identify a new biomarker for the diagnosis of OLP and the possibility of malignant transformation, further study of the different types of miRNA expression profile is necessary.

Functional Role of miRNAs in OLP

OLP is classified as an oral potentially malignant disorder (OPMD) that has no known cause. It is a T cell-mediated autoimmune disease. During its occurrence and development, miRNA regulation cannot be ignored. Below, we summarize a few such miRNAs, including their potential targets and mechanisms, according to their expression in OLP (Table 1).

miR-214

Among vertebrates, miR-214 is substantially conserved, and it is among a family of miRNA precursors.³⁶ The human miR-214 gene is found in intron 14 of the Dynamin-3 gene in the chromosomal region 1q24.3.³⁷ MiR-214 is an osteoclast-derived miRNA molecule that can suppress bone formation.³⁸ Four mature miRNAs can be generated with the primary transcript of miR-214: miR-214-3p and miR-199-5p from the leading strand and miR-214-5p and miR-199-3p from the passenger strand.³⁹ MiR-214 was first identified as a factor that was biologically linked to the death of the cell, and its expression may lower apoptosis in HeLa cells.⁴⁰ It is involved in a wide range of biological processes, such as the embryonic development of the retina, muscles, neurons, and pancreas. In addition, it is implicated in controlling various critical physiological processes, such as immune tolerance of dendritic cells, hepatic gluconeogenesis, and angiogenesis.³⁶ One study reported that the level of miR-214-3p was lower in a control group and that miR-214-3p may be a risk factor for MS.⁴¹ miR-214 has both tumor suppressor and oncogenic activities in melanoma, breast cancer, and ovarian cancer.⁴² In the oral cavity, by targeting the β -catenin gene CTNBN1, miR-214 may regulate the Wnt/ β -catenin signaling pathway, thus participating in mechanisms underlying the differentiation of periodontal ligament stem cells.⁴³ In addition, a recent study explored the influence of miR-214 on the proliferation and apoptosis of oral cancer cells.⁴⁴ By sponging miR-214, circFOXO3 may upregulate the expression of lysine demethylase 2A (KDM2A), which promotes tumor progression in OSCC.⁴⁵ LncRNA HOXA11-AS promotes cisplatin resistance and the proliferation of OSCC by suppressing miR-214-3p expression,⁴⁶ which indicates that miR-214 may play an essential role in the development of oral illnesses. CD44 is a multifunctional cell receptor that regulates vascular gene activation in proatherogenic environments and inflammatory gene production in macrophages and conveys a cancer phenotype.⁴⁷ In mucosa samples of patients with OLP, a direct link has been found between CD44 expression and miR-214 expression; that study also found that CD44 is the direct target of miR-214, confirming that low levels of miR-214 are associated with OLP and are possible candidate molecules for drug development.⁴⁸

miR-146a

Dr. David Baltimore's lab published the first report on human miR-146a in 2006. The miR-146a gene is found on chromosome 11 in mice, and it is found on chromosomes 5, 10, and 19 in humans.^{49,50} MiR-146a is implicated in the differentiation, inflammation, and function of adaptive and innate immune cells,⁴⁹ and it also has substantial regulatory involvement in a number of immune cells, including T cells, B cells, and dendritic cells. The physiopathology of various

Table 1 MiRNAs are Involved in Regulating Oral Lichen Planus

MiRNA	Targets	Expression	Function
miR-214	CD44	-	As a tumor suppressor; reduced miR-214 is associated with OLP
miR-146a	STAT1, IFN- γ , IL-2	+	DQ786243 may regulate the induction and function of CD4+ Treg cells through Foxp3/miR-146a/NFkB axis; Foxp3 and miR-146a regulate the progression of OLP bynegatively regulating TRAF6
miR-155	SOCS1	+	A positive feedback loop of miR-155 and IFN- γ might contribute of the Th1-dominated immune response in EOLP
miR-27a/b	TGF- β , p53, p63, Smad	-	Vitamin D/VDR signaling may control miR-27a/b expression to exert its physiological actions in OLP
miR-26a/b	PKC δ / CD38	-	The suppression of vitamin D/VDR pathway decreases miR-26a/b for anti-OLP

Note: Upregulation: +; Downregulation: -.

Abbreviations: CD44, CD38, cell surface glycoprotein; STAT1, signal transducer and activator of transcription I; IFN- γ , interferon-gamma; IL-2, interleukin-2; SOCS1, suppressor of cytokine signaling 1; TGF- β , transforming growth factor beta; P53, P56, tumor suppressor protein; Smad, protein; PKC, protein kinase C.

immunologically based inflammatory diseases may be influenced by miR-146a.^{51,52} MiR-146a works as a differentiation inhibitor for human T helper type 1 cells (Th1-cells) by interacting with the protein kinase C epsilon (PRKC), and it controls Th1-cell development in human CD4+T cells as part of a functional complex composed of signal transducers and transcriptional activators 4 and PRKC.⁵⁰ Its involvement in the beginning and progress of numerous kinds of cancers has been reported, including prostate and esophageal cancer,⁵³ and it promotes the proliferation, migration, and invasion by OSCC cells.⁵⁴ One study found that miR-146a-5p exhibits upregulated expression in OSCC, and inhibits transcriptional activity, performing a carcinogenic function in OSCC.⁵⁵ In another study, the expression of miR-146a was not obviously different between peripheral blood T cells and a control group; however, it was higher in local lesions of OLP patients. As a necessary regulator of Treg cells, forkhead box P3 (FOXP3) acts as a mediator of inflammation and immune response and is overexpressed in OLP.⁵⁶ Wang et al⁵⁷ demonstrated that by regulating miR-146a, FOXP3 influenced cell proliferation and the apoptosis of lipopolysaccharide (LPS)-incubated HaCaT cells and raised Treg cells in CD4+T cells derived from individuals with OLP. By modulating its target gene, TNF receptor-associated factor 6 (TRAF6), miR-146a alone can control LPS-incubated HaCaT cells. These findings suggest that in OLP, miR-146a may be necessary for the local immune response and may be usable as a biomarker to evaluate the severity of OLP.

miR-155

MiR-155 is derived from an exon of the B-cell integration cluster gene,^{58,59} miR-155 host gene.⁶⁰ It is one of the most multifunctional and conservative miRNAs, and it has a variety of functions and is connected to tumor development, immunological modulation, and inflammation.^{61,62} miR-155 deficiency can cause a disorder of immune system response.⁶³ In MS, insulin resistance and poor glycemic control are linked to the dysregulation of miR-155.⁶⁴ MiR-155 is elevated in oral submucous fibrosis tissues, and its suppression may help alleviate persistent myofibroblast activation by upregulating its direct target, mammalian target of rapamycin complex 1.⁶⁵ In oral cancer cells, the expression of FOXO3a is upregulated by the inhibition of miR-155 expression, which also increases cell apoptosis and inhibits cell growth.⁶⁶

MiR-155 may be linked to OLP. Liang et al⁶⁷ found that miR-155 might play an important role in the pathogenesis of OLP. Through transcriptional control of immunologically relevant genes, IFN- γ coordinates a vast variety of cellular activities.⁶⁸ IFN- γ may limit the synthesis of anti-inflammatory cytokines, such as IL-10 and IL-4, while boosting the secretion of proinflammatory cytokines such as IL-2.^{69,70} In Hu et al, miR-155 was closely linked to the severity of OLP, and ELOP patients' peripheral blood had a high level of expression of miR-155. miR-155 may be upregulated by inflammatory cytokines such as INF- γ , TNF- α , TGF- β 1, and IL-1 β . The expression of miR-155 is upregulated by IL-2 and IL-15. Other proinflammatory triggers, such as LPS—which activates Toll-like receptor 4 in macrophages and dendritic cells, as well as bleomycin—can also activate miR-155. Conversely, IL-10 is a powerful inhibitor of miR-155. In addition, in EOLP CD4 +T cells, positive feedback loops for miR-155 and IFN- γ have been discovered that could lead to Th1-dominated immune responses; in the feedback loop, miR-155 may negatively regulate suppressor of cytokine signaling 1 (SOCS1). The most likely target of miR-155 is SOCS1.⁷¹ Further, it has been found that the deregulation of miR-155/endothelial nitric oxide synthase may be responsible for an elevated risk for OLP.⁷² Therefore, miR-155 is vital for investigating pathogenesis in OLP.

miR-27a/b

The structures of miR-27a and miR-27b are generated from subtypes of miR-27 encoded on various chromosomes.⁷³ miR-27 participates in the proliferation of various cells, including myocytes, neuroblastoma cells, and T cells.^{74–76} By degrading mRNA, miR-27a can inhibit both protein and mRNA levels of the target genes and can control gene expression.⁷⁷ MiR-27b functions differently in pathological and physiological environments.⁷³ A large body of evidence suggests that miR-27b is mainly regulated through transcriptional regulation of multiple molecules and signaling pathways through epigenetic changes and genomic loss (including DNA methylation and histone modification).⁷⁸ MiR-27b-3p is a crucial mediator of human adipogenesis, so it is also crucial to MS.⁷⁹

In OSCC, F-box and WD repeat domain containing 7 inhibit miR-27a-regulated cell proliferation and invasion through the epithelial-mesenchymal transition (EMT) and the PI3K/AKT signaling pathway.⁸⁰ In tongue squamous cell carcinoma (TSCC) tissues and cell lines, miR-27b expression is considerably reduced, and the expression of miR-27b has been linked to cancer status. MiR-27b hampers TSCC migration and proliferation by suppressing the EMT process and

targeting integrin subunit alpha 5 (ITGA5).⁸¹ In studies on OLP, the expression of miR-27a/b was lower than in controls, suggesting that signaling suppression may be the reason for the reduction of miR-27a/b, and that miR-27a/b may take part in the immune response.^{82,83} Polo-like kinase 2 (PLK2) is related to cell proliferation and apoptosis.⁸⁴ When miR-27b targets PLK2, it stimulates the proliferation of oral keratinocytes.⁸⁵ Peptidyl prolyl isomerase F, also called CypD, is associated with apoptosis. The reduction of miR-27b-3p may be the reason for increased CypD protein levels and lead to OLP basal epithelial apoptosis.⁸⁶ One study noted its potential as a biomarker for miR-27b.⁸⁷ Therefore, investigation of miR-27a/b is vital for comprehending the pathogenesis of OLP.

miR-26a/b

The human miR-26 family includes miR-26a, miR-26b, miR-4465, and miR-1297, which are all highly conserved miRNAs.⁸⁸ Two distinct loci produce the mature version of miR-26a: on human chromosome 3p21.3, miR-26a-1 is found at the intron of the C-terminal domain (CTD) small phosphatase-like (CTDSPL) gene; on human chromosome 12q14.1, miR-26a-2 is located in the intron of the CTD small phosphatase (CTDSP)2 gene.⁸⁹ On chromosome 2, miR-26b is found in the fourth intron of the CTDSP1 gene.⁹⁰ In addition, miR-26 has been implicated in various developmental and physiological functions, including neuronal differentiation, muscle development, and hepatic glucose and lipid metabolism.⁹¹⁻⁹⁵ It is significantly downregulated, and PAK1 (PAKs are a family of serine/threonine kinases that function at downstream nodes in a variety of oncogenic signaling pathways) is highly expressed in TSCC tissues and cells. In addition, *in vitro*, acquiring miR-26a or miR-26b blocks cell glycolysis, invasion, migration, and cycle, but the inhibition of PAK1 promotes apoptosis, and miR-26a/miR-26b overexpression inhibits the proliferation of TSCC tumors.

The above results indicate that miR-26 takes part in tumor inhibition and may be the therapeutic target of TSCC patients.⁹⁶ Furthermore, recent investigations have demonstrated that miR-26b inhibits the IL-6, TNF- α , and NF- κ B pathways in bronchial epithelial cells, suggesting that it has a role in regulating inflammatory responses, which can reduce the number of biopsies taken from patients with OLP.^{97,98} Du et al⁹⁹ found that OLP patients have lower levels of miR-26, and this may be due to the inhibition of the vitamin D/vitamin D receptor (VDR) pathway. In the oral keratinocyte microenvironment, PKC δ is an essential regulator of apoptosis action, while CD38 is an inflammatory marker, and PKC δ is related to the activity of CD38. Thus, by targeting CD38, miR-26 may also reduce inflammation. Therefore, higher miR-26 levels tend to result in better anti-OLP results. However, that conclusion is not definitive and further studies should be conducted to ensure the efficacy of miR-26 for the treatment of OLP.

Other miRNAs also play a vital role in OLP. In OLP mucosa, the expression of the putative target cyclin D1 (CCND1) is increased when miR-138 is suppressed, and by targeting CCND1, miR-23a-3p might be a regulator of proliferation and inflammatory response. This suggests that miR-138 and miR-23a-3p may play critical roles in pathogenesis and thus, for patients with OLP, be promising new therapeutic targets.^{100,101} Aghbari et al¹⁰² reported that in the oral mucosa of OLP patients, there is a negative association between the tissue expression of miR-137 (reduced) and that of CD8 (elevated). In addition, in CD4+ T cells, increased miR-29b interacts with IFN- γ through a regulatory feedback loop, causing widespread DNA hypomethylation, which alters the immunological response of Th1-cells. This ultimately contributes to the immune dysregulation of OLP.¹⁰³

Signaling Pathway in the OLP

The biological functions of miRNAs have not yet been fully identified. However, many studies of miRNAs associated with human diseases have suggested that these molecules play an essential role in controlling cellular pathways. They are known to be involved in various signaling pathways, such as vitamin D/VDR, NF- κ B, and PI3K/AKT/mTOR that may also be critical therapeutic targets for OLP (Figure 2).

Vitamin D/VDR Signaling Pathway

Vitamin D is an essential factor involved in the regulation of inflammation, immune response, and carcinoma inhibition via the action of its receptor VDR.¹⁰⁴ The VDR endocrine system has been discovered in nearly all nucleated cells.¹⁰⁵ Hypoxia inducible factor 1 subunit alpha (HIF-1 α) is a heterodimeric transcription factor.¹⁰⁶ LPS promotes the HIF-1 α

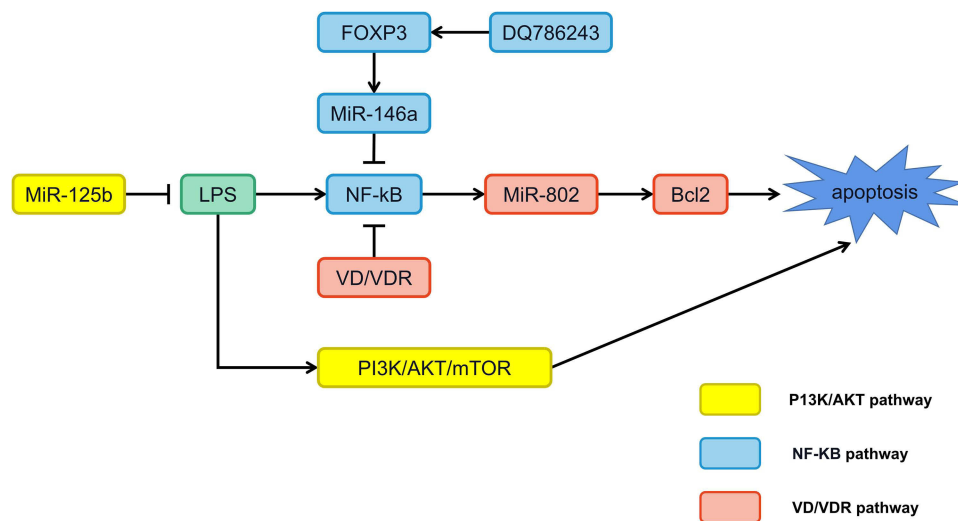


Figure 2 MiRNAs participate in the regulation of oral lichen planus through multiple signaling pathways.

Abbreviations: DQ786243, lncRNA; FOXP3, forkhead box P3; LPS, lipopolysaccharide; Bcl2, B-cell lymphoma 2.

state by activating the nuclear factor- κ B (NF- κ B) pathway in myeloid cells and increasing the level of succinic acid in macrophages;^{107,108} the induced HIF-1 α is thought to boost transcription of cytokines, including IFN- γ and IL-1 β in immune cells, thus speeding up inflammatory response.^{109,110} Von Hippel-Lindau (VHL) and prolyl hydroxylase (PHD) are critical factors required for HIF-1 α proteasome degradation.¹⁰⁶ LPS inhibits the expression of VHL in human oral keratinocyte (HOK), but not PHD1 or PHD2, suggesting that VHL may play a protective role in inflammatory diseases.¹¹¹ Vitamin D is a critical regulator that attenuates endotoxin-induced HIF-1 α in a VHL-dependent manner and inhibits lipopolysaccharide-induced HIF-1 α , thereby blocking IFN- γ and IL-1 β production. Mechanically, the NF- κ B pathway is inactivated by vitamin D, which increases VHL levels, resulting in a decrease in HIF-1 α .¹¹¹ In oral keratinocytes, vitamin D/VDR signaling protects cells by suppressing cytokine production and apoptosis in OLP.^{111,112} By decreasing VDR expression, miR-122 can improve the apoptosis of oral keratinocytes.¹⁶ In addition, the vitamin D/VDR signaling pathway inhibits the expression of miR-802 in human oral keratinocytes that is stimulated or activated by lipopolysaccharides, thereby inhibiting the apoptosis of OLP cells by blocking the NF- κ B signaling pathway.¹¹² Ge et al⁸² found that the expression of miR-27 in OLP is accelerated by vitamin D/VDR signaling. Vitamin D enhances VDR in oral epithelial cells when paired with VDREs, improving miR-27 transcription. Therefore, vitamin D/VDR signaling suppression may be at least partially responsible for the lowering of miR-27 in OLP. Although the mechanisms of miR-27 reduction have been elucidated, its involvement in the development of OLP requires extensive investigation to explain the etiology of OLP.

NF- κ B Signaling Pathway

NF- κ B, which was identified in 1986, is a transcription factor that binds to enhancer elements of the activated B cell immunoglobulin kappa light chain. It is made up of a group of transcription factors that play a vital role in controlling a broad range of biological responses.¹¹³ Due to its function in regulating pro-inflammatory genes, such as cytokines, chemokines, and adhesion molecules, the NF- κ B pathway is traditionally considered to be a typical pro-inflammatory signaling pathway.^{114,115} The relative abundances of bacteria in the genera *Derxia*, *Haemophilus*, and *Pseudomonas* tend to be lower, and the expression levels of TLR4, NF- κ B p65, IL-6, and TNF- α are higher, in OLP patients. Changes in microbial composition ratio may initiate the TLR4-NF- κ B inflammatory signaling pathway and play a role in OLP lesions.^{116,117} In addition, as stated earlier, through the FOXP3/miR-146a/NF- κ B axis, lncRNA DQ786243 regulates the induction and function of CD4⁺ Treg cells in OLP.¹¹⁸ DQ786243 and Foxp3 expression are highly upregulated in OLP patients compared to controls. This indicates that DQ786243 and Foxp3 dysregulation may play a role in the development of OLP. In addition, there is a positive association between DQ786243 and

Foxp3, which implies that DQ786243 influences the expression of Foxp3, and dysregulation of DQ786243 is implicated in the progression of OLP by altering Foxp3⁺ Treg cells. Foxp3⁺ Treg cells keep the immune system in check by inhibiting various inflammatory responses; DQ786243 overexpression-induced Foxp3⁺ Treg cells show an extraordinary inhibitory ability to restrict T cells from proliferating. In addition, Foxp3 regulates miR-146a, which governs the course of OLP; the overexpression of DQ786243 increases miR-146a expression, which is inhibited by Foxp3 reduction. MiR-146a reduces the expression of interleukin 1 receptor associated kinase 1 and TRAF6, inhibiting NF- κ B activation. In addition, the expressions of pI κ B- α and p-p65 are dramatically reduced by DQ786243 overexpression.

The above findings suggest that DQ786243 dysregulation plays a crucial role in regulating Treg cells in OLP through the Foxp3/miR-146a/NF- κ B axis, which implies a new way of looking at how OLP develops and a prospective therapeutic method for OLP. In addition, NF- κ B can be restrained by total glucosides of paeony (TGP) and influence the production of inflammatory cytokines; additionally, TGP can increase the expression of miR-214 and p-STAT3 and improve the immunomodulatory function of mesenchymal stem cells. The connection between these observations is also worth looking into.^{119,120}

PI3K/AKT/mTOR Signaling Pathway

In numerous human malignancies, the PI3K/AKT/mTOR signaling pathway is typically activated, and metastasis, angiogenesis, metabolism, growth, proliferation, and survival are only a few of the cellular mechanisms it controls.^{121,122} Many autoimmune and inflammatory illnesses have also been found to feature IGF1 as a critical regulator.¹²³ A previous study reported elevated IGF1 mRNA expression in OLP peripheral T cells and activation of the AKT/mTOR pathway in local OLP lesions.^{124,125} The activation of the IGF1 and PI3K/AKT/mTOR pathways and aberrant autophagy may govern crosstalk between T cells and keratinocytes and contribute to the pathogenesis of OLP.¹²⁶ In LPS-incubated HaCaT cells, a reduction of miR-125b may enhance the phosphorylation of Akt and its downstream target mTOR protein, underlining the role of the dysfunctional PI3K/Akt/mTOR signaling pathway in the malignant potential of OLP.¹²⁷ Lc3B is found in the membranes of autophagosomes, plays a crucial function in autophagosome production, and is a reliable marker of autophagy. MiR-122 and miR-199 directly target AKT1 and mTOR, miR-122 overexpression inhibits the expression of AKT1 and Lc3B, and miR-199 overexpression reduces the levels of Lc3B and mTOR. Hence, miR-199 and miR-122, by modulating the expression of mTOR and AKT1, may have a role in the pathogenesis of OLP, and miR-122 and miR-199 may be potential targets for use in the treatment of OLP.¹²⁸ Bioinformatics analyses have suggested that miR-34a-5p can modulate OLP progression through the PI3K/Akt signaling pathway and may be a potential biomarker.¹²⁹

Although the cellular biology of these pathways is well documented regarding cell growth and the pathophysiology of many diseases, the mechanics of these pathways in OLP are poorly understood. Although the exact regulatory mechanisms involved in miRNAs and these proteins remain unclear, miRNAs play a vital part in the progression of OLP, and more research is needed to understand how miRNA networks influence the complexity of OLP through signal transduction pathways.

Future Expectations

In a previous article, we reported on the activity of a few miRNAs in OLP and their potential function in pathogenesis. There is no doubt that miRNAs play a significant role in OLP; the study and exploration of miRNAs may be crucial for diagnosis and treatment.

The clinical characteristics of oral squamous moss (including its symmetry distribution) have led some researchers to suggest that making a correct diagnosis is enough, particularly in the case of common skin lesions. However, to validate clinical diagnoses and rule out hyperplasia and malignant tumors, oral biopsy is usually recommended, combined with a histopathological examination.¹³⁰ Some OLP patients refuse to undergo biopsy, so there is an urgent need for a noninvasive and accurate tool to aid clinical diagnosis.

OLP is caused by an immune system malfunction that produces precancerous lesions. Therefore, despite the availability of traditional biopsy methods, new identification procedures are necessary.¹³¹ Among cytokines, TNF- α and IL are thought to be feasible biomarkers for OLP diagnosis and prognosis.¹³² In contrast with other potential

biomarkers that predict OLP, there is growing evidence that misregulated miRNAs can cause (or can be associated with) carcinogenesis in OLP. A biomarker is a molecule that can be utilized to diagnose and predict the prognosis of a disease. Sensitivity and durability are among the most critical features of a useful biomarker. Biomarkers can be obtained in a relatively painless manner. Recent findings show that miRNAs can be used as biomarkers in the diagnosis of some diseases and are viable therapeutic targets. Therefore, they may become valuable biomarkers in OLP diagnosis. However, it should be noted that most studies have been single-center retrospective studies and have generally been underpowered cohort studies. As a result, many non-overlapping and even conflicting reports have been published. These differences are largely due to biological and technical differences between the starting materials (purified cell types of cells using control population RNA extraction) and technology platforms (microarray qRT-PCR and next-generation sequencing) used in the studies, as well as differences in the different statistical methods used.¹³³ One study that performed microarray analysis of miRNAs in patients with OLP and healthy controls found significant changes (more than two-fold differences) in the expression of about 70 miRNAs.²⁸ However, clinical studies have involved only a small number of patients or healthy controls, so larger study cohorts and live animal models are needed to identify the best new biomarkers.

In recent years, cytokine treatment has become a prominent research focus, and preliminary studies have demonstrated its efficacy. At present, many miRNA-related therapies are being investigated.¹³⁴ Several immune-related proteins—including vascular endothelial growth factor, FOXP3, toll-like receptors, matrix metalloproteinase 9, and others—have been documented in patients with OLP.^{28,135} MiRNAs have been linked to these immune-related proteins in basic tests for clinical inflammatory diseases or research in molecular biology. In addition, due to the human body's high tolerance for it and its assistance in confirming the targeting of specific cells, miRNA may be a more ideal drug carrier than liposomes.¹³⁶ OLP is a complex, multifactorial disease that leaves us with many unanswered questions. The radical treatment of OLP requires intensive treatment, but complications can still occur because there is currently no way to block multi-signal carcinogenic pathways and the adverse reactions caused by drugs. Therefore, new therapeutic strategies need to be developed to improve clinical outcomes and quality of life. Targeting oncogenes and downstream signaling proteins with miRNAs could prove to be a breakthrough in the treatment of OLP.

Although many experimental investigations incorporating miRNA therapies have been undertaken over the years, only a few miRNA therapeutics have reached clinical development. Choosing the most appropriate miRNA candidates or miRNA targets for each type of illness is one of the most challenging issues in creating miRNA-based treatments. Among the other obstacles are developing miRNA delivery vehicles that provide better stability to the treatment candidate and enable tissue-specific targeting, as well as minimizing potential toxicities and off-target effects.¹³⁷ Many questions concerning the pathogenesis of OLP remain unanswered. Obtaining a deeper understanding of the role of the miRNA-mRNA-cytokine pathway in the pathogenesis of OLP will be a milestone for future treatments. In addition, such discoveries may be helpful in single-gene therapy.

Conclusion

Numerous cytokines have been implicated in the development of OLP, and miRNAs may play a role in the normal inflammatory response and immune function. However, the regulatory pathways of miRNA-mRNA in OLP remain unclear, and a great deal of work needs to be done to understand the molecular mechanisms of miRNAs and OLP fully. We reviewed research on several important miRNAs, and also examined the role of miRNA in several signaling pathways. This review may serve as a foundation for future research and contribute to the study of OLP pathogenesis. Further in vitro and animal model studies are needed to explore miRNA therapies for OLP.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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