

Review Article

Retinoid Treatment for Oral Leukoplakia: Current Evidence and Future Development

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Oral leukoplakia (OLK) is one of the most common oral potentially malignant disorders (OPMDs). Preventing malignant transformation is the main purpose of OLK treatment. The treatment approaches of OLK include surgery, chemotherapy, and other therapies, such as photodynamic therapy and CO₂ laser. The application of genomic variation-based chemotherapy in OLK deserves further exploration. As chemopreventive drugs, drug resistance and disease recurrence have limited their use in OLK. In this review, we concentrate on the retinoid treatment for OLK, summarizing the current status of retinoids in the treatment of OLK, the mechanism of retinoid action, and the mechanisms of resistance to retinoid therapy, and we highlight the strategies to improve retinoid efficacy in the treatment of OLK, such as the combination of retinoids and epigenetic regulators or metabolism-blocking agents, new synthetic retinoids, and new drug delivery systems of retinoids, providing new methods for the successful clinical application of retinoids in the treatment of OLK.

1. Introduction

The cancerization of oral mucosa is a multistage and multistep process, and the risk of oral squamous cell carcinoma (OSCC) is relatively increased in patients with some oral lesions called oral potentially malignant disorders (OPMDs) [1]. Oral leukoplakia (OLK) is one of the most common OPMDs, which is characterized by epithelial hyperkeratosis and dysplasia. This disease tends to occur in men over the age of 40, and the incidence is higher in smokers. Alcohol consumption and human papillomavirus (HPV) infection also contribute to the occurrence of OLK [2]. Some patients with OLK have a trend of malignant transformation, and the overall malignant transformation rate of OLK is reported to vary between 1.1% and 40.8% [3]. Risk factors for malignant transformation of OLK include female sex, long disease course, nonsmoker, location on the tongue or floor of the mouth, size over 200 mm², nonhomogeneous leukoplakia, *Candida albicans* infection, and presence of oral epithelial dysplasia (OED) [4].

The main purpose of OLK treatment is to prevent malignant transformation. It is recommended that OLK patients should remove irritants and receive regular follow-up examinations. Treatment approaches include surgery, chemotherapy, and other therapies, such as photodynamic therapy and CO₂ laser. It was previously thought that surgery was an effective means to prevent the malignant transformation of OLK. However, in recent years, the concept of field cancerization has become widely accepted [5], which suggests that the underlying genetic alterations may be more extensive than the morphological or histological abnormalities. Therefore, even if the clinically obvious lesions can be removed, the original genetically altered mucosal tissue is still preserved; thus, local recurrence and malignant transformation cannot be prevented. Furthermore, owing to the existence of important anatomical structures in the oral cavity, surgery may not be the best treatment for OLK [6]. Compared to surgery, photodynamic therapy (PDT) and CO₂ lasers are minimally invasive therapies [7], but they also fail to prevent oral carcinogenesis

due to the field cancerization effect. Surprisingly, those who are male, homogenous type, nonsmokers, and nondrinkers appeared to display a higher propensity for malignancy after laser surgery [8, 9]. Therefore, chemotherapy may be a more desirable approach. Vitamin A and its metabolite retinoids are the most important candidates for OLK chemotherapy. It has been shown that 13-cis-retinoic acid (13-cis-RA, isotretinoin) at high doses can prevent second primary tumors in patients treated for head and neck squamous cell carcinoma [10], and the chemoprevention of OLK deserves further study.

Vitamin A is a generic term for a group of lipophilic isoprenoids comprising a cyclic group and a linear chain with a hydrophilic polar group. Vitamin A itself cannot perform its physiological function until it is converted to its active forms which are called retinoids. Retinoids refer to a group of signaling molecules related to vitamin A, including its natural and synthetic metabolites or analogs. The basic chemical structure of retinoid molecules consists of a cyclic end group, a polyene side chain, and a polar end group. Natural forms include retinyl esters, retinol, retinal, and retinoic acid. Vitamin A is a fat-soluble vitamin that is mainly stored in the liver and adipose tissue in the form of retinyl esters. In blood, it can bind to retinol-binding protein and transthyretin to form a protein complex that circulates in blood. Retinol can enter cells and be irreversibly oxidized to its active forms: all-trans retinoic acid (ATRA, tretinoin), 9-cis-retinoic acid (9-cis-RA), and 13-cis-RA. In addition, efforts have been made to synthesize new retinoids with less toxicity and better efficiency.

Retinoids are essential regulators of many physiological processes in the human body. They play important roles in animal embryogenesis and organogenesis and simultaneously regulate tissue homeostasis, cell proliferation, cell differentiation, and apoptosis. Retinoid signaling is critical for cells (especially epithelial cells) to maintain normal proliferation and differentiation [11–14]. Thus, they are widely used in treating skin diseases, central nervous system diseases, and metabolic diseases. Moreover, in the past few decades, researchers have conducted a large number of studies on retinoids *in vitro* and *in vivo* and found that they can inhibit or reverse the occurrence and development of cancers, including hematological malignancies, as well as solid tumors of the oral cavity, breast, lung, prostate, bladder, liver, skin, and colon [15, 16]. In addition to the applications above, as chemopreventive agents, retinoids have also been used in some precancerous lesions, such as OLK, cervical dysplasia, and xeroderma pigmentosum [17].

It is worth mentioning that ATRA has an excellent effect on acute promyelocytic leukemia (APL). APL has a characteristic (15; 17) (q22; q12-21) chromosomal translocation, which leads to the promyelocytic leukemia gene (PML) fusing with the retinoid receptor gene (RAR α). The PML-RAR α fusion oncoprotein acts as a transcriptional inhibitor to block normal myeloid differentiation. Pharmacological doses of ATRA can act on RAR α and induce remission of the disease. In particular, the combined application of ATRA and arsenic trioxide (ATO) allows the complete remission rate of APL to reach 90%, transforming APL from a highly fatal disease to a highly curable disease [18].

Despite the great remission results for APL, the effects of retinoids on solid cancers and precancerous lesions are still controversial, and the condition is the same in OLK. Previous clinical practice has proven that retinoids have a curative effect on OLK, but their clinical application is still limited for various reasons such as retinoid resistance. Therefore, in this review, we concentrate on the retinoid treatment for OLK, summarizing the current status of retinoids in the treatment of OLK, the mechanism of retinoid action, and the mechanisms of resistance to retinoid therapy, and we highlight the strategies to improve retinoid efficacy in the treatment of OLK, such as the combination of retinoids and epigenetic regulators or metabolism-blocking agents, new synthetic retinoids, and new drug delivery systems of retinoids, providing new methods for the successful clinical application of retinoids in the treatment of OLK.

2. Current Status of Retinoids in the Treatment of OLK

Retinoids are among the most well-studied chemopreventive agents. Thousands of retinoids have been artificially synthesized, but the types used in clinics are still very limited. There are two types of retinoids widely used in the clinical treatment of cancer: ATRA for acute promyelocytic leukemia and 13-cis-RA for neuroblastoma. In oral diseases, clinical trials have been carried out mainly including two kinds of natural retinoids (ATRA, 13-cis-RA) and a synthetic form: N-(4-hydroxyphenyl) retinamide (4-HPR, fenretinide) (Table 1).

Some early studies found that vitamin A has a significant antikeratosis effect, and it has been proven to have a good effect on vulvar leukoplakia and senile keratosis. Since oral leukoplakia is also a disorder of keratinization, in 1958, Mulay and Urbach [30] conducted a clinical trial in which they applied vitamin A tablets topically to 10 patients with typical OLK. The results showed significant remission in 70% of patients, thus indicating the therapeutic potential of vitamin A in OLK patients.

The researchers then began to evaluate the efficacy of retinoids. When patients with OLK were given 13-cis-RA at 1-2 mg/kg/d for three months, significant reductions in lesion size were observed in 67% (16/24) of the drug group, and dysplasia was reversed in 54% (13/24) of patients. However, 2-3 months after treatment, 56% (9/16) of patients who reached remission had relapsed [26]. In addition to systemic administration, some researchers have also evaluated the efficacy of the topical application of retinoids, which can achieve higher drug concentrations in the target tissues and reduce general toxicity. Shah et al. [21] treated 16 patients with OLK using 13-cis-RA in the form of oral lozenges at varied concentrations; 55% (6/11) of patients demonstrated complete remission and 27% (3/11) of them demonstrated partial remission. Relapse occurred in 2 patients with complete remission, and the patient who had no recurrence also showed histologic and cytologic regression. In several later experiments, ATRA at a 0.05% concentration was often topically used to treat OLK [19, 20]. However, Scardina et al. [23] reported that the topical use of 13-cis-RA at 0.18% concentration is more effective and has no side effects compared to

TABLE 1: Current status of retinoids in the treatment of OLK.

Agent	Strategy of application	Study design	Patients	CR (%)	PR (%)	R (%)	Reference
ATRA	Topical 0.05% ATRA gel, 4 times daily for a mean of 3.5 years, follow-up at a mean of 23 months	Noncomparative	26	27	NA	40	[19]
	Topical 0.05% ATRA cream, 2 times daily for 5 weeks, follow-up at 4 months	Noncomparative	20	80	0	NA	[20]
13- <i>cis</i> -RA	Oral 13- <i>cis</i> -RA lozenges, 3/5/10 mg/d for 6 months	Noncomparative	16	27	55	67	[21]
	Oral 13- <i>cis</i> -RA, 50–70 mg/d for 3 months	Noncomparative	10	0	30	NA	[22]
	Topical 0.05%/0.18% 13- <i>cis</i> -RA, twice daily for 3 months, follow-up at 10 years	Randomized, dose-response controlled, double-blinded	40	NA	NA	NA	[23]
	Topical 0.1% 13- <i>cis</i> -RA gel, 3 times daily for 4 months	Randomized, placebo controlled, double-blinded	15	21	79	NA	[24]
	Topical 0.1% 13- <i>cis</i> -RA gel, 3 times daily for 4 months	Randomized, placebo controlled, double-blinded	10	11	89	NA	[25]
4-HPR	Oral 13- <i>cis</i> -RA, 1–2 mg/kg/d for 3 months, follow-up at 6 months	Randomized, placebo controlled, double-blinded	44	NA	NA	56	[26]
	First phase: oral 13- <i>cis</i> -RA, 1.5 mg/kg/d for 3 months Second phase: oral β -carotene (30 mg/d) or isotretinoin (0.5 mg/kg/d) for 9 months	Noncomparative	70	NA	NA	NA	[27]
4-HPR	Oral 4-HPR, 200 mg/d for 3 months (a monthly 3-day drug holiday)	Noncomparative	35	0	34	NA	[28]
	Four cycles of 4-HPR 900 mg/m ² orally twice daily days 1 through 7, repeated every 3 weeks	Noncomparative	15	0	20	NA	[29]

CR, complete response; PR, partial response; R, recurrence; NA, not available.

the 0.05% concentration. Meanwhile, it was reported that the use of oral 13-cis-RA rinses is helpful in reducing the recurrence rate of OSCC and dysplasia after using other treatments [31]. Synthetic retinoids such as 4-HPR have also been examined in OLK, and several reports have shown that it can induce cell differentiation at low concentrations and apoptosis at higher concentrations in cancer cells in vitro. However, in the treatment of OLK, increasing the concentration of 4-HPR did not improve its efficacy [29], which may be related to the low concentration in the oral target tissue. Furthermore, 4-HPR induces apoptosis by generating reactive oxygen species [32], and oral precancerous lesions have stronger antioxidant capacity; thus, increasing the dose does not produce apoptosis. Some clinical trials on the efficiency of retinoids in OLK patients are summarized in Table 1. We can see that the lack of controls and the small sample size affect the reliability of some data. In the future, high-quality clinical trials should be conducted. The sample size should be expanded, and the experimental design should be optimized (randomized, controlled, blind, multicenter, etc.). In addition, reasonable diagnostic criteria, inclusion criteria, exclusion criteria, effectiveness evaluation indices, and safety evaluation indices are needed.

Retinoids regulate cell proliferation, differentiation, and apoptosis, so researchers hope that they can treat OPMDs, especially abnormal keratinization diseases such as OLK. However, the efficacy of retinoids in OLK is not particularly satisfactory; some OLK patients show retinoid resistance and cases with complete remission also have a high recurrence rate. Long-term research and follow-up found that they have limited effects on preventing the malignant transformation of OLK. At the same time, they exhibit obvious side effects, sometimes even more than the pain caused by the disease itself, so patients have to discontinue treatment. For example, systemic administration of retinoids can cause hypertriglyceridemia, dry skin/mucous membranes, erythema, itching, cheilitis, headache, and hair loss [22, 33]. A burning sensation at the application site often occurs when the agent is used topically. Furthermore, the teratogenicity of retinoids should also not be ignored [34, 35]. Therefore, using the existing retinoids solely to treat OLK, especially when used in large doses, is not advisable. Thus, we should seek new strategies to combat their resistance and reduce side effects [24, 25, 27, 28].

3. Retinoid Signaling and Mechanisms of Retinoid Action

Retinoids can be divided into endogenous and exogenous retinoids. Endogenous retinoids are derived from the diet and are then transformed into their active forms (retinoic acid). Retinoic acid and other exogenous retinoids can enter the nucleus and bind to some nuclear receptors or affect the extranuclear signaling pathway to play their roles (Figure 1).

3.1. Retinoid Signaling. As mentioned earlier, retinoids are a class of compounds linked to vitamin A. Mammals cannot synthesize vitamin A de novo and must obtain it from their diet. (1) Preformed vitamin A (retinol, retinal, retinoic acid,

and retinyl esters) is found in animal products (meat, eggs). (2) Provitamin A carotenoids (β -cryptoxanthin, α -carotene, β -carotene, and γ -carotene) are found in plant foods [36].

Dietary vitamin A such as retinyl esters and β -carotene can be packaged into chylomicrons and transported into the bloodstream, where they can be taken up by target cells via lipoprotein-specific receptors. The most important resource of retinoids is β -carotene, which can be transformed into retinal by the action of β , β -carotene-15,15'-monooxygenase (BCMO1) in the gut or in the target cells; it is then converted into retinol by retinal reductase (RALR). Retinol can be absorbed in the proximal small intestine with the help of bile acids. Through the action of lecithin retinol acyltransferase (LRAT), it is esterified to retinyl esters which are the most important storage forms of retinoids in the liver. When needed, it can be transformed back to retinol by retinyl ester hydrolase (REH) [37]. Retinol, the main circulating form of vitamin A, travels in the bloodstream through binding to retinol-binding protein (RBP) and transthyretin (TTR). Through a transmembrane protein named STRA6 (stimulated by retinoic acid-6), the membrane receptor for RBP4, target cells can take up retinol.

Upon entering a target cell, retinol binds to cellular retinol-binding proteins (CRBPs), which are delivered to enzymes that transform it into retinoic acid. First, alcohol dehydrogenase or retinol dehydrogenase (ADH/RDH) reversibly oxidizes retinol to retinal. Next, acetaldehyde dehydrogenase (ALDH) irreversibly converts retinal to retinoic acid (ATRA, 9-cis-RA, 13-cis-RA), and ATRA can be isomerized to 9-cis-RA or 13-cis-RA isomers through a non-enzymatic process; it is the most transcriptionally active isomer [38]. In cells, the enzyme cytochrome P450 (CYP450) can degrade retinoic acid to mostly inactive compounds, and binding to intracellular lipid-binding proteins (ILBPs) can prevent retinoic acid degradation, which is conducive to their migration to the nucleus, where they bind to specific nuclear receptors to activate the transcription of target genes.

3.2. The Mechanisms of Retinoid Action. Retinoids can exert genomic and nongenomic effects. The genomic effects are regulated by coactivators and corepressors, which can change the structure of chromatin and then affect the accessibility of retinoid receptors to target DNA, thus activating or repressing the transcription of target genes. The nongenomic effect depends on the extranuclear signaling pathway and is closely related to genomic effects.

3.2.1. Genomic Effects of Retinoids. The genomic effects of retinoids are mainly mediated by nuclear receptors. Retinoid receptors are involved in ligand-activated nuclear receptors (NRs), which are ligand-regulated transcription factors that bind DNA sequence-specific motifs in enhancers and promoters of target genes to control their transcription. They share a common structural organization that contains a variable N-terminal domain, a DNA-binding domain (DBD), and a ligand-binding domain (LBD) [39]. They function as monomers, homodimers, or heterodimers. Two types of retinoid receptors are known in humans: retinoic acid

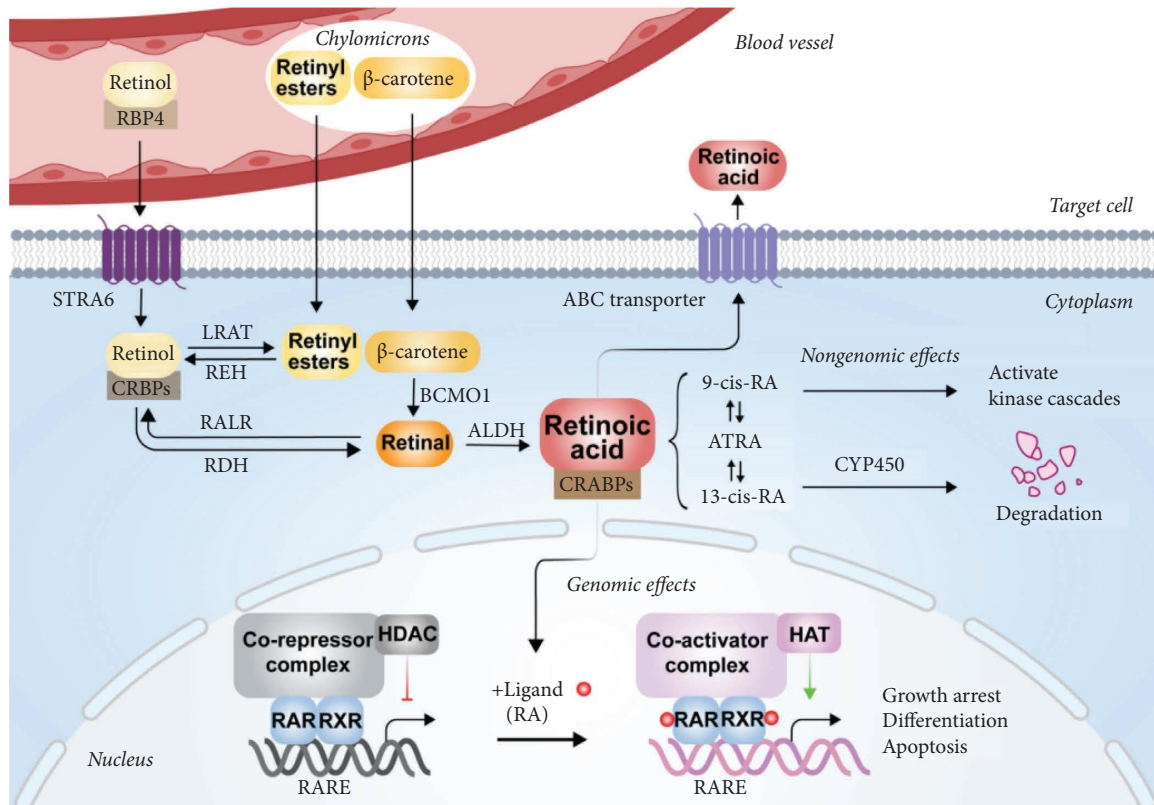


FIGURE 1: The metabolism and mechanism of retinoids. Retinol travels in the bloodstream through binding to retinol-binding protein (RBP) and transthyretin (TTR). Through a transmembrane protein named STRA6, target cells can take up retinol into target tissues. Upon entering a target cell, retinol binds to cellular retinol-binding proteins (CRABPs), which are delivered to enzymes that transform it into retinoic acid. First, alcohol dehydrogenase or retinol dehydrogenase (ADH/RDH) reversibly oxidizes retinol to retinal tissue. Next, acetaldehyde dehydrogenase (ALDH) irreversibly converts retinal to retinoic acid (ATRA, 9-*cis*-RA, 13-*cis*-RA). Retinoic acid can then enter the nucleus to exert genomic effects. In the absence of ligands, RARs repress gene transcription by recruiting corepressors, and HDACs can remove acetyl groups from nucleosome histones, which can lead to chromatin condensation, prevent binding of other factors, and cause transcriptional silencing of the target gene. After ligand binding, RARs undergo structural changes, including the dissociation of corepressor complexes and the recruitment of coactivators. Histone acetyltransferases (HATs) can bring about epigenetic changes and chromatin depolymerization so that target genes can be normally transcribed. They can also activate kinase cascades to exhibit additional nontranscriptional effects or be degraded under the action of CYP26 enzymes.

receptors (RARs) and retinoid X receptors (RXRs). Each nuclear retinoid receptor consists of three isoforms (α , β , γ), which have distinct amino- and carboxy-terminal domains. Each RAR isoform has different subtypes, and their A regions are different. RAR α and RAR γ have two subtypes (RAR α 1, RAR γ 1, RAR α 2, and RAR γ 2), while RAR β has five subtypes (RAR γ 1–4 and 10). All isoforms of RXR have two subtypes (1, 2) [40]. ATRA and 13-*cis* RA can bind to RAR, while 9-*cis* RA can bind to RARs and RXRs.

RAR can form a RAR/RXR heterodimer with RXR, which can bind to retinoic acid response elements (RAREs) consisting of tandem 5-AGGTCA-3 sites called DR1–DR5 [16]. The RAR/RXR heterodimers mainly function by recruiting transcriptional cofactors, including corepressors and coactivators. These cofactors act as adaptors to bring ligand-bound NRs to chromatin so that NRs can control the transcription of target genes [41]. The position of the H12 α -helix on the LBD determines the types of cofactors (corepressors or coactivators), and its position is determined by the ligands [42].

In the absence of ligands, RARs repress gene transcription by recruiting corepressors, including NR corepressor (N-CoR) and thyroid hormone receptor (SMRT), which promote the recruitment of complexes containing histone deacetylase (HDAC). HDACs are able to remove acetyl groups from nucleosome histones [43], which can lead to chromatin condensation, prevent binding of other factors, and cause transcriptional silencing of the target gene.

After ligand binding, RARs undergo structural changes, including the dissociation of corepressor complexes and the recruitment of coactivators such as NCOA/SRC/p16 and CREBBP/CBP [44, 45]. These coactivators can alter the chromatin structure around target gene promoters, thereby recruiting histone acetyltransferases (HATs) or histone demethylases (HDMs), histone methyltransferases (HMTs), and ATP-dependent SWItch/Sucrose Nonfermentable (SWI/SNF) chromatin remodeling complex, which is responsible for chromatin depolymerization and transcriptional activation.

RXR can form a homodimer or bind to other receptors, such as the vitamin D receptor (VDR), the peroxisome proliferator-activated receptor (PPAR), and the thyroid hormone receptor (TR) [46]. RXR does not directly bind coactivators, but its “subordination” relationship in heterodimers plays a critical role in avoiding confusion in signaling pathways; however, the molecular mechanism is still unclear [44].

Two ILBPs, cellular retinoic acid-binding protein-II (CRABP-II) and fatty acid-binding protein 5 (FABP5), in the body can bind to retinoids and deliver them to nuclear receptors, thereby regulating the transcription of target genes [47]. Studies have found that CRABP-II transmits them to RAR, while FABP5 transmits them to PPAR β/δ . The transcriptional activation of RAR results in the inhibition of cell growth, and the activation of PPAR β/δ promotes the expression of survival genes and stimulates cell proliferation. Therefore, the biological effects of retinoids may depend on the CRABP-II/FABP5 ratio [48].

Studies have identified more than 500 possible target genes for retinoids. Retinoids directly regulate target genes through the binding of receptor heterodimers to RARE, and it has been proven that more than 20 genes are regulated through this pathway, while other target genes may be regulated indirectly [49].

3.2.2. Nongenomic Effects of Retinoids. Retinoids can also activate kinase cascades, thereby exhibiting additional non-transcriptional effects that interact with genomic effects [50]. Different cell lines may activate different kinase cascades [45]. For example, studies have shown that retinoids can rapidly activate the p38 MAPK/MSK1 pathway, and the initiated phosphorylation cascade can promote the recruitment of the RAR α /TFIIH complex to the target promoter to control the transcription of RAR α [51]. Subsequent studies found that RAR α existing in membrane lipid rafts can form complexes with G protein α Q (G α Q), and the rapid formation of RAR α /G α Q complexes in lipid rafts induced by retinoids is the basis for the activation of p38 MAPK [52]. Retinoids can also activate extracellular signal-regulated kinase 1/2 (ERK1/2) pathways and phosphatidylinositol-3-kinase (PI3K) and then influence the function of RAR [50]. In OSCC and oral dysplasia cell lines, ATRA can suppress STAT3 signaling by increasing JAK2 and decreasing ERK1/2 in a time- and dose-dependent manner, consequently inhibiting proliferation and inducing apoptosis [53]. Although the exact mechanism of the nongenomic effects of retinoids remains to be fully understood, we gradually discovered that the deregulation of certain signaling pathways in tumor cells may be associated with retinoid resistance, and it is undeniable that these effects also play important roles.

4. Mechanisms of OLK Resistance to Retinoid Therapy

Retinoids can promote differentiation and apoptosis, as well as have antiproliferative and antioxidant activities. Retinoids seem promising in a subset of solid tumors and precancerous

lesions, but most studies with sufficient follow-up have found merely transitional effects, even within tumor types such as gastric cancer [54] and breast cancer [55]; the condition is the same in OLK. Retinoid resistance can be divided into two types: intrinsic or acquired, and it is the result of numerous factors. Therefore, we reviewed the most common changes in retinoid function and metabolism that may be responsible for resistance to retinoid therapy (Figure 2).

4.1. Alterations of Retinoid-Related Receptors. Retinoids mainly rely on binding to nuclear receptors to exert their effects. In some diseases, these receptors are altered. For example, the receptor gene may be mutated, resulting in variations in gene expression, and posttranslational modifications (e.g., phosphorylation) can affect receptor action, all of which are able to cause receptor dysfunction and drug resistance.

Alterations of RAR typically occur in hematological malignancies. In APL, mutations in the RAR α region of the PML-RAR α gene are present in cases of acquired resistance and may be mechanistically involved in retinoid resistance [56]. However, these patients remain sensitive to ATO therapy [57]. Meanwhile, phosphorylation can also regulate RAR function. Deregulation of cytoplasmic signaling cascades can lead to aberrant phosphorylation of RAR, resulting in resistance to retinoids. As mentioned earlier, the activation of p38MAPK by retinoids is essential to the transcription of RAR α [51]. In ERBB2-positive human breast cancer, the p38MAPK/MSK1 pathway is deregulated, so they show no response to retinoids [58]. In non-small-cell lung cancer (NSCLC) cell lines, Akt is normally activated, which can phosphorylate RAR α and inhibits its transcriptional activation [59].

RAR β expression was found to be downregulated in many kinds of solid tumors and precancerous lesions. For example, researchers have used *in situ* hybridization to compare the expression of retinoid receptors in head and neck squamous cell carcinomas, dysplastic lesions, adjacent normal tissues, and normal volunteer tissues [60]. They found that only approximately 70% of adjacent normal and hyperplastic lesion specimens expressed RAR β mRNA, and its expression was further reduced to 56% in dysplastic lesions and to 35% in head and neck squamous cell carcinoma (HNSCC). This change has also been observed in esophageal cancer [61], NSCLC [62], and breast cancer [63, 64]. The expression of RAR β is lost in oral precancerous lesions and can be restored by isotretinoin therapy [65]. Meanwhile, the introduction of the RAR β gene into retinoic acid-insensitive breast cancer cell lines can restore retinoic acid sensitivity [66]. Toulouse et al. transfected RAR α 1, RAR β 1, and RAR β 2 into the lung cancer cell line Calu-1 and only the overexpression of RAR β 2 sensitized these cells to retinoids. The stable overexpression of RAR α 1 and β 1 did not show the same effect [67]. Therefore, it is reasonable to speculate that RAR β 2 is a key receptor mediating the growth-inhibitory effect of retinoids.

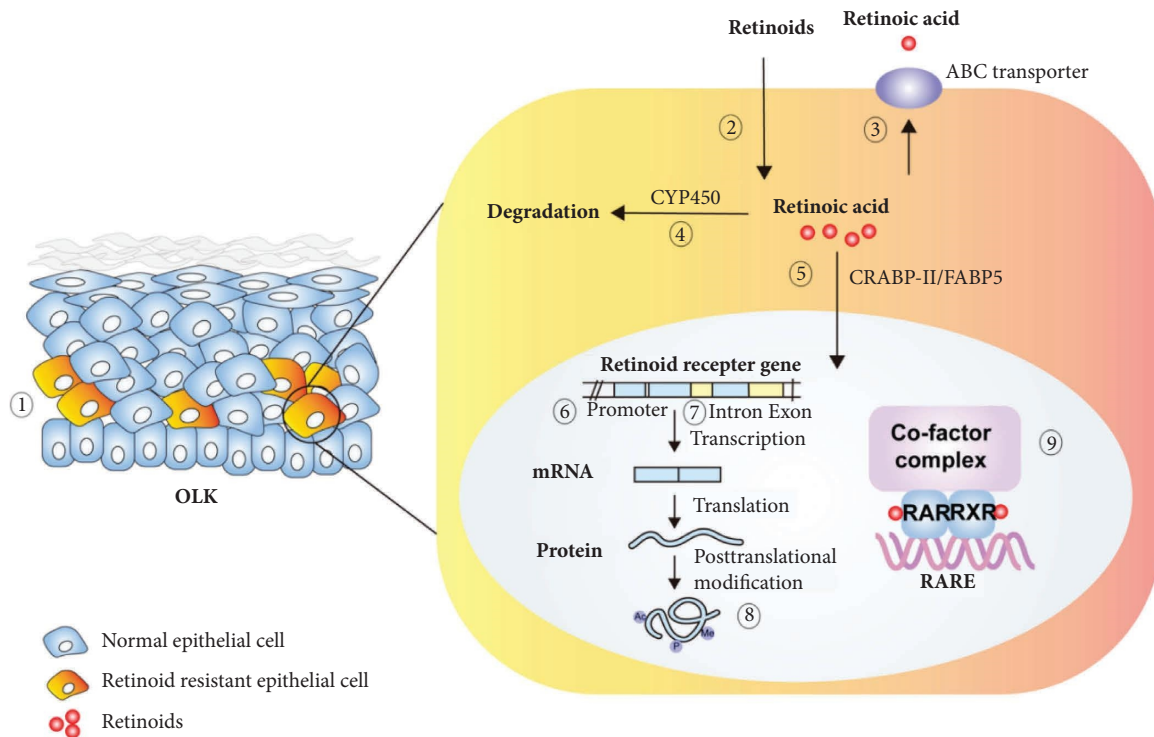


FIGURE 2: Potential synergistic pathways of retinoid resistance. Retinoid resistance may be related to (1) stem accumulation of OLK epithelial cells, (2) decreased production of endogenous retinoids or low retinoids concentrations in target cells, (3) increased retinoids efflux, (4) increased degradation of retinoids, (5) low CRABP-II/FABP5 ratio, (6) epigenetic changes (e.g., DNA hypermethylation and repressive histone modifications), (7) mutations in retinoid-related receptors, (8) changes in posttranslational modification (e.g., abnormal phosphorylation), and (9) cofactors alterations.

Later work showed that the suppressed expression of $RAR\beta 2$ may be related to gene silencing due to epigenetic changes. The concept of epigenetics was first proposed by Conrad Waddington in 1942 [68] and is characterized by stable and heritable changes in gene expression not affecting the DNA sequence [69], including DNA methylation, histone covalent modification, chromatin remodeling, and the roles of noncoding RNAs and polyclonal proteins in gene expression. It has been found in many studies that epigenetic changes are the basis for the occurrence of many cancers, which may serve as a possible direction for the diagnosis and treatment of cancer [70]. Youssef et al. demonstrated that 53% (66/124) of OLK specimens showed methylation of CpG islands in the $RAR\beta 2$ promoter [71]. This phenomenon was also found in breast cancer [72], cervical cancer [73], HNSCC [74], and colon cancer [75]. Petty et al. determined the methylation level of the $RAR\beta$ P2 promoter in retinoic acid-sensitive (BEAS-2B) and retinoic acid-resistant (BEAS-2B-R1) HBE cells to investigate whether hypermethylation inhibits $RAR\beta 2$ expression in HBE cells [76]. They observed hypermethylation in the 3' region of the $RAR\beta$ P2 promoter in BEAS-2B-R1 cells, while this phenomenon was not observed in BEAS-2B cells. Moreover, the treatment of BEAS-2B-R1 cells with a DNA demethylating agent-*azacitidine* (5-azacitidine, 5-AzaC) alone or in combination with retinoids can restore $RAR\beta 2$ expression. In APL, through the recruitment of DNA methyltransferases to target promoters,

the PML-RAR fusion protein induces gene hypermethylation, resulting in gene silencing [77]. In t (8; 21) acute myeloid leukemia (AML), the AML1/ETO fusion protein promotes leukemia by recruiting a class I repressor complex containing histone deacetylase (HDAC) to AML1 target gene promoters [78]. In addition, there has been some evidence that loss of $RAR\beta$ expression was linked to abnormal histone H3 acetylation in thyroid cancer [79], lung cancer [80], and cervical cancer [81].

In addition, $RAR\gamma$ and RXR also play a significant role in mediating drug resistance to retinoids. Loss of $RAR\gamma$ predisposes mice to cutaneous squamous cell carcinoma, and knockout of $RAR\gamma$ abrogates retinoid-induced cycle arrest and keratinocyte apoptosis [82]. The expression of $RAR\gamma$ mRNA was significantly downregulated in OSCC and OLK cell lines [83]. Further studies have shown that $RAR\gamma$ can mediate the growth-inhibitory effect of retinoids and influence retinoid turnover in HNSCC [84], while $RAR\beta$ mediates the inhibitory effect of ATRA on squamous cell differentiation in HNSCC without enhancing its growth-inhibitory effect [85, 86]. Compared with ovarian cancer cell lines with reduced levels of single $RAR\alpha$ or $RXR\alpha$, ovarian cancer cell lines acquired the greatest retinoid resistance by reducing the levels of both $RAR\alpha$ and $RXR\alpha$ [87]. Wu et al. found that $RXR\alpha$ contributes to mediating the growth inhibition of retinoids on ovarian cancer cells [88]. The roles of $RAR\gamma$ and RXR in OLK remain to be further investigated.

4.2. Accumulation of Stemness Features of OLK Epithelial Cells. Epithelial cells typically exhibit plasticity when exposed to noxious stimuli, thereby promoting tissue regeneration. Plasticity includes the interconversion of different stem cell pools, the activation of facultative stem cells, and the dedifferentiation, transdifferentiation, or phenotypic transformation of differentiated cells. When it is abnormally activated, it can promote the malignant transformation and confer tumorigenic properties to epithelial cells [89]. These cells with the potential for renewal and multidirectional differentiation are called tumor stem cells (CSCs) [90, 91]. In OPMDs and HNSCC, the accumulation of cancer-deriving molecules in epithelial or tumor cells can sustain cancer stemness characteristics. For example, SOX-2 is one of the key regulators of transcription and induction of pluripotency of stem cells. Luiz et al. have found a higher expression of SOX-2 in the OLK group compared to the control group [92]. Other markers of CSCs, such as NANOG, have also been highlighted in OLK [93]. CSCs can induce resistance to various chemotherapeutic drugs through metabolic reprogramming, upregulated drug efflux proteins, and protective autophagy [94]. In APL, retinoids combined with ATO can promote the differentiation of tumor cells and thereby inhibit cancer progression [18]. Therefore, targeting these cells is a promising strategy to overcome the retinoid resistance of OLK.

4.3. Changes in Retinoid Metabolism Pathway. Several diseases can lead to changes related to retinoid metabolism, which can accelerate its degradation, prevent it from entering the nucleus to bind to retinoid-related receptors, or even cause it to be excreted from the cells. These changes reduce the effective concentration of retinoids, resulting in drug resistance.

4.3.1. Intracellular Transport of Retinoids. As mentioned earlier, in cells, retinoids can bind to proteins such as CRABP-II and FABP5 which can mediate their effects. Studies have found that the expression of some lipid-binding proteins is associated with retinoid resistance; for example, CRABP-II overexpression markedly increased MCF-7 breast cancer cell sensitivity to retinoid-induced growth inhibition. The reduction in CRABP-II expression made these cells resistant to retinoids [95]. In medulloblastoma cells, it was demonstrated that the downregulation of CRABP-II was due to abnormal methylation. Therefore, the authors of this study proposed detecting the expression or methylation of CRABP-II so that targeted combination therapy can be used for patients with medulloblastoma and other types of cancers [96]. However, although the demethylation agent 5-Aza-2'-deoxycytidine (5-Aza-CdR) can enhance CRABP-II expression, the recovery of CRABP-II expression or the increase in the CRABP-II/FABP5 ratio does not seem to overcome the ATRA resistance of COLO 16 cells [97]. Likewise, similar conclusions were drawn in glioblastoma [98]. Therefore, the resistance of cutaneous squamous cell carcinoma and glioblastoma to retinoids may need to be explained by other molecular mechanisms. Conversely,

studies have been found to reduce the FABP5/CRABP-II ratio in breast tissue, the transfer of retinoids from PPAR β/δ to RAR can inhibit tumor growth [99]. Likewise, in APL, there is no causal relationship between CRABP-II expression (or retinoic acid-binding activity) and acquired retinoid resistance, whereas FABP5/CRABP-II may play a role in APL cell responses to retinoids [100]. The relationship between the CRABP-II/FABP5 ratio and retinoid resistance in OLK needs to be further studied.

4.3.2. Efflux of Retinoids. The efflux of retinoids from cells also reduces their intracellular concentration. Proteins that belong to the ATP-binding cassette (ABC) transmembrane transporter superfamily are highly conserved among all species. Using ATP as an energy source, they function as transporters to export signaling molecules and drugs. In many cases, the overexpression of ABC transporter genes contributes to multidrug resistance (MDR). For example, studies have found that in neuroblastoma (NBL) cell lines, cells overexpressing multidrug resistance protein 1 (MRP1) are more resistant to ATRA treatment [101]. High expression of MRP1 has also been observed in OSCC, which promotes drug resistance to several chemotherapy drugs [102], including retinoids. A study found that a higher TM rate is observed in OLK patients who demonstrate positive expression of the ATP-binding cassette, G2 subfamily (ABCG2) [103]. Considering that retinoid signaling plays an important role in maintaining normal proliferation and differentiation of epithelial cells, we suspect that high ABCG2 may lead to changes in retinoid signaling in some patients with OLK, but this hypothesis remains to be investigated.

4.3.3. Increased Degradation of Retinoids. In the early stage of using ATRA to treat APL, some patients will relapse early after ATRA treatment. Researchers have found that the body will automatically induce accelerated ATRA clearance after repeated administration, so the effective plasma concentration of ATRA cannot be maintained during continuous treatment, thus explaining part of the ATRA resistance [104]. Later studies found that this autoinduction is usually mediated by CYP26A1 in the liver. The researchers also developed a PBPK model after ATRA administration, which helped in the design of new dosing regimens and the development of a new generation of retinoid metabolism-blocking agents (RAMBAs) [105].

CYP26 enzymes have been identified as the major retinoid clearance enzymes and can also be involved in tumor progression. For instance, the upregulation of CYP26A1 expression has been observed in HNSCC [106] and breast cancer [107], which promotes rapid drug clearance after sustained oral administration and is associated with retinoid resistance. It was reported that two types of HNSCC cell lines show increased expression of CYP26 A1 mRNA, indicating the quick metabolism of retinoids, which is related to carcinogenesis [106]. The same mechanisms may occur in OLK. Several recent studies have shown that CRABP-I and CRABP-II can also affect the metabolism of ATRA by

interacting with CYP26 enzymes [108, 109]. In myeloid and promyelocytic leukemia cells, RAR α has been reported to regulate CYP26 expression, which may be related to some feedback mechanisms, and a RAR α -specific antagonist (CD2503) can completely block CYP26 mRNA expression in NB4 cells and HL-60 cells [110].

5. Strategies to Improve Retinoid Efficacy

Retinoids are critical molecules in biological differentiation therapy, but patients with OLK respond differently to retinoid therapy, which has seriously limited their wide application. Therefore, breaking through resistance and enabling their curative effects have become urgent problems to be solved. Although there is currently no comprehensive solution, drug combinations, new synthetic retinoids, and new methods of drug administration may be useful (Figure 3).

5.1. Combination of Retinoids and Epigenetic Regulators. As mentioned above, the downregulation of RAR β expression in solid tumors is mainly associated with some epigenetic changes that lead to gene silencing. Therefore, it is possible to consider combining retinoids with some epigenetic regulators to improve their efficacy, such as DNA methyltransferase inhibitors (DNMTi) or histone deacetylase inhibitors (HDACi). McGregor et al. found that 5-Aza-CdR can reverse the immortality phenotype of dysplasia [111]. Combined use of 5-Aza-CdR and ATRA induced RAR β re-expression in immortalized OPMDs [112]. Similarly, in HNSCC cells, by combining the histone deacetylase inhibitors trichostatin A (TSA) and ATRA, it is possible to enhance the growth-inhibiting effects and greatly increase transcriptional activation of the RAR β promoter, thereby breaking resistance to retinoids [113].

Moreover, these epigenetic regulators can not only remove some unfavorable epigenetic modifications but also help to eradicate CSCs. Studies have shown that 5-Aza-CdR can effectively inhibit prostate cancer tumorigenesis by targeting CSCs [114]. Inhibition of HDAC can destroy CSCs in HNSCC [115]. Therefore, the combination of these two drugs can counteract retinoid resistance in two ways.

5.2. Combination of Retinoids and Retinoic acid metabolism-blocking agents (RAMBAs). RAMBAs, including ketoconazole, liarozole, and talarozole, can increase endogenous retinoids or counteract auto-induced resistance to retinoid therapy. Liarozole may upregulate RAR β in HNSCC [116], but its effect in combination with retinoids for oral diseases remains to be evaluated. R116010, another highly specific CYP26 inhibitor, has shown clinical benefits in breast cancer [117] and NBL [118]; however, its role in OLK is currently unknown. A detailed introduction to RAMBAs can be found in the review article by Nelson et al. [119]. Although RAMBAs are not currently approved for the clinical treatment of precancerous lesions, numerous preclinical studies have observed their potential to break through retinoid resistance. The synergies of retinoids and RAMBAs in OLK await further study.

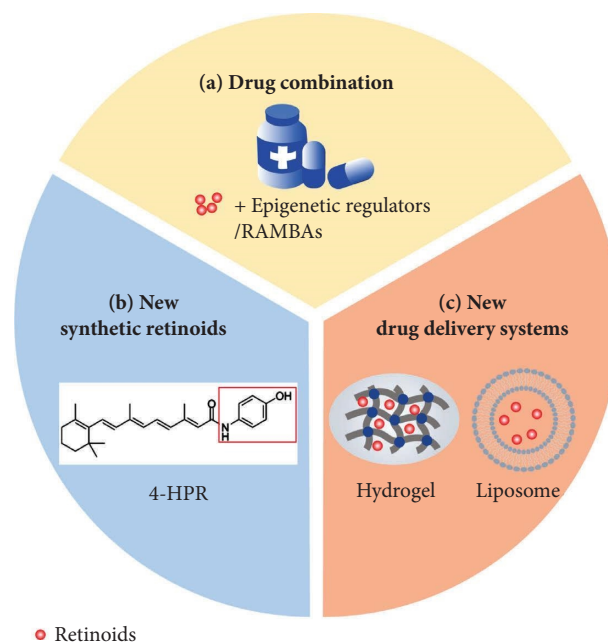


FIGURE 3: Possible strategies to overcome retinoid resistance in OLK treatment. The following measures may help to overcome retinoid resistance. (a) Drug combination (e.g., epigenetic regulators, RAMBAs), (b) new synthetic retinoids, and (c) new drug delivery systems.

5.3. New Synthetic Retinoids. In addition to improving the efficacy of natural retinoids, researchers are also working to synthesize new retinoids. Because the expression of RAR β is mostly downregulated in HNSCC and part of OLK, retinoids with retinoid receptor-independent activities or target receptors other than RAR β have raised hopes. For example, researchers have evaluated the effects of *bexarotene* (a synthetic RXR agonist) and *CD1530* (a synthetic specific RAR γ agonist), and the combination of these two drugs can prevent oral cancer induced by the carcinogen 4-NQO and does not cause serious changes in blood lipids [120]. These two novel retinoids can target RXR and RAR γ , so even if the expression of RAR β is lost, they can also exert a tumor suppressor effect. Moreover, *LGD1550* can decrease cell proliferation in HNSCC in part by interfering with TGF- α /EGFR autocrine signaling [121].

4-HPR, a synthetic retinoid, has been found to exhibit dual effects. At low concentrations, it induces differentiation of cells that is dependent on RAR, while at high concentrations, it increases apoptosis independent of RAR [28, 32]. Moreover, its clearance is relatively slow in the human body. Some clinical trials have also been carried out in OLK, but their efficacy has yet to be improved.

5.4. New Drug Delivery Systems of Retinoids. When administered systematically, retinoids have high affinities for multiple sites during the absorption process, so researchers are committed to designing novel drug delivery systems to increase the concentration of retinoids at the target site. Nanomedicine has been developed as an immunotherapy for oral diseases. Compared with free ATRA, PLGA-PEG

nanoparticles loaded with ATRA and modified with an anti-TP-L1 antibody can enhance the stability and chemotherapeutic efficacy in OSCC and oral dysplasia and reduce systemic side effects [122].

Topical administration via the oral mucosa has many special advantages, allowing drugs to avoid problems with gastrointestinal tract degradation and hepatic first-pass metabolism and to be absorbed faster. Owing to the continuous dilution by saliva, extending the residence time of medication in the oral cavity becomes the greatest challenge. Over the years, researchers have strived to use polymers in drug delivery systems to improve drug adhesion on the oral mucosa [123]. Several traditional and novel drug delivery systems (hydrogels, polymeric nanoparticles, liposomes, electrospun nanofibers, etc.) have shown potential in the treatment of oral diseases [124]. The isoG-TA and G-TA hydrogels even have the potential to delay the malignant transformation of OLK [125]. Therefore, for retinoid-based therapy of OLK, many attempts could be made to develop advanced systems to optimize retinoid bioavailability.

5.5. Other Strategies. Given that the combination of ATRA and ATO for the treatment of APL produces a synergistic effect by enhancing the apoptotic process [16], similarly, we speculate that the poor efficacy of retinoids in solid tumors may also be related to the overexpression of several apoptosis-inhibiting factors, so combining retinoids with drugs that induce apoptosis, such as sulindac, may improve their effects [126].

Preferentially expressed antigen of melanoma (PRAME) is a competitive inhibitor of RA at RAR that can significantly repress RAR signaling [127]. Compared to normal oral cells or tissues, prominent PRAME expression was observed in HNSCC and some OPMDs [128]. Thus, combining PRAME vaccine/antibody or adoptive T-cell therapy with retinoids shows promise as an effective measure for retinoid-resistant OSCC and OPMDs [129].

6. Summary and Prospective

Here, we review the biochemical and molecular mechanisms by which the retinoid signaling pathway operates and describe the efficacy of retinoids in OLK. We highlight the main causes of retinoid resistance, and possible strategies for overcoming resistance are discussed to provide a theoretical basis for future research.

Resistance to retinoid therapy is still a major challenge in the treatment of solid tumors and precancerous lesions. Over the past few years, a great deal of research has been conducted, but the results are not satisfactory. The causes of retinoid resistance remain unclear, which requires further study of the mechanisms to explain how the retinoid signaling pathway influences cell growth or differentiation and how the retinoid signaling pathway changes during the tumorigenesis process. Cellular heterogeneity is consistently the main reason for drug resistance. Thus, in the future, we can apply emerging technologies, such as single-cell sequencing or CyTOF, to comprehensively explore the heterogeneity among precancerous

lesions, identify previously unknown cell types, and discover potentially drug-resistant cells, which will facilitate the development of more effective, targeted, and personalized retinoid treatments for OLK patients. Moreover, if we determine how retinoids are regulated, we can promote the production of endogenous retinoids instead of exogenous retinoids to enhance their specificity and eliminate any unwanted side effects. In the treatment of OPMDs, the traditional administration methods of retinoids include systemic and topical administration. The side effects of systemic administration are significant. When administered topically, an effective concentration cannot be guaranteed for a long time on account of the continuous dilution by saliva. Therefore, it is important to improve the drug delivery systems of retinoids to optimize bioavailability and minimize systemic toxicities. Moreover, changing the medication strategy may be beneficial to improve the long-term efficacy of retinoids. Intermittent administration or low-dose maintenance after the lesions disappear may be useful, but we must fully test the impact of the long-term application of retinoids on the body and the oral mucosa. In addition, the appropriate maintenance dose and suitable dosing interval should be determined.

Data Availability

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yuting Hu wrote the original draft and visualized the study. Yuting Hu, Ying Wang, and Ying Li conceptualized the study. Yu Zhou, Jing Li, Xin Zeng, and Qianming Chen wrote, reviewed, and edited the article.

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