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Targeting LZK in Oral Squamous Cell Carcinoma: A Review of Local PROTAC Delivery via Dissolving Microneedles

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Abstract. Oral squamous cell carcinoma (OSCC) is the predominant histological type of oral cancer, with a continuously increasing disease burden and unsatisfactory long-term survival. c-MYC and gain-of-function mutant p53 (GOF-p53) are important oncogenic factors in OSCC/head and neck squamous cell carcinoma (HNSCC), but both remain difficult to target directly. Leucine zipper-bearing kinase (LZK) can maintain c-MYC stability through kinase-dependent mechanisms and stabilize GOF-p53 through non-kinase-dependent scaffold functions. Proteolysis-targeting chimera (PROTAC)-mediated degradation of LZK may simultaneously block its catalytic and non-catalytic functions; however, this strategy is limited by the large molecular size, poor membrane permeability, and restricted systemic delivery of PROTAC molecules. Dissolving microneedles (DMNs) may enable local delivery and reduce systemic exposure. This review summarizes recent advances in LZK-PROTAC and dissolving microneedle-mediated delivery, and discusses their potential value as postoperative adjuvant therapy for stage I-II OSCC.

Keywords: oral squamous cell carcinoma, LZK, PROTAC, dissolving microneedles, local delivery

1. Introduction

Oral squamous cell carcinoma (OSCC) accounts for more than 90% of oral malignant tumors and represents the predominant histological type of oral cancer. In recent years, the disease burden of oral cancer and lip and oral cavity cancer in China has shown an upward trend. Long-term survival remains unsatisfactory, and local recurrence, regional metastasis, and treatment-related functional impairment remain important prognostic factors [1, 2]. Current OSCC treatment is based primarily on surgical resection, combined with radiotherapy, chemotherapy, or immunotherapy according to tumor stage and risk factors. For patients with stage I-II disease, surgery is usually the main treatment modality; however, postoperative minimal residual disease and local recurrence risk may persist, whereas intensified chemoradiotherapy may cause toxicities disproportionate to the expected benefit. Therefore, the development of low-toxicity, precise, and locally repeatable adjuvant therapeutic strategies has clinical relevance.

Using a narrative review approach, this article summarizes and analyzes studies on OSCC-related molecular targets, LZK-PROTAC degradation strategies, and dissolving microneedle-mediated local delivery. The review focuses on the mechanistic rationale for LZK as a potential upstream target,

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recent progress in LZK-PROTAC development, and the prospects and future validation requirements of dissolving microneedle-based local delivery for postoperative adjuvant therapy in OSCC.

2. Therapeutic rationale for targeting c-MYC, GOF-p53, and LZK in OSCC

2.1. c-MYC and GOF-p53: important but difficult-to-target oncogenic factors in OSCC

At the molecular level, c-MYC and gain-of-function mutant p53 (GOF-p53) are important oncogenic factors in OSCC/HNSCC. c-MYC is a key transcription factor that promotes cell-cycle progression, metabolic reprogramming, apoptosis resistance, and therapy resistance [3]. GOF-p53, which often arises from missense mutations in TP53, not only loses tumor-suppressive activity but also acquires oncogenic functions that promote proliferation, invasion, and treatment resistance [4-6]. However, both proteins are difficult to target directly. c-MYC is an intrinsically disordered protein (IDP), lacks a stable drug-binding pocket, and must heterodimerize with MAX (Myc-associated factor X) before binding E-box elements to exert its transcriptional activity [7, 8]. GOF-p53 is characterized by diverse mutation types and marked conformational heterogeneity, which limits the development of universal targeting strategies. Therefore, identifying upstream nodes that can simultaneously regulate c-MYC and GOF-p53 represents an important direction in OSCC-targeted therapy research.

2.2. LZK: an upstream therapeutic node linking c-MYC and GOF-p53

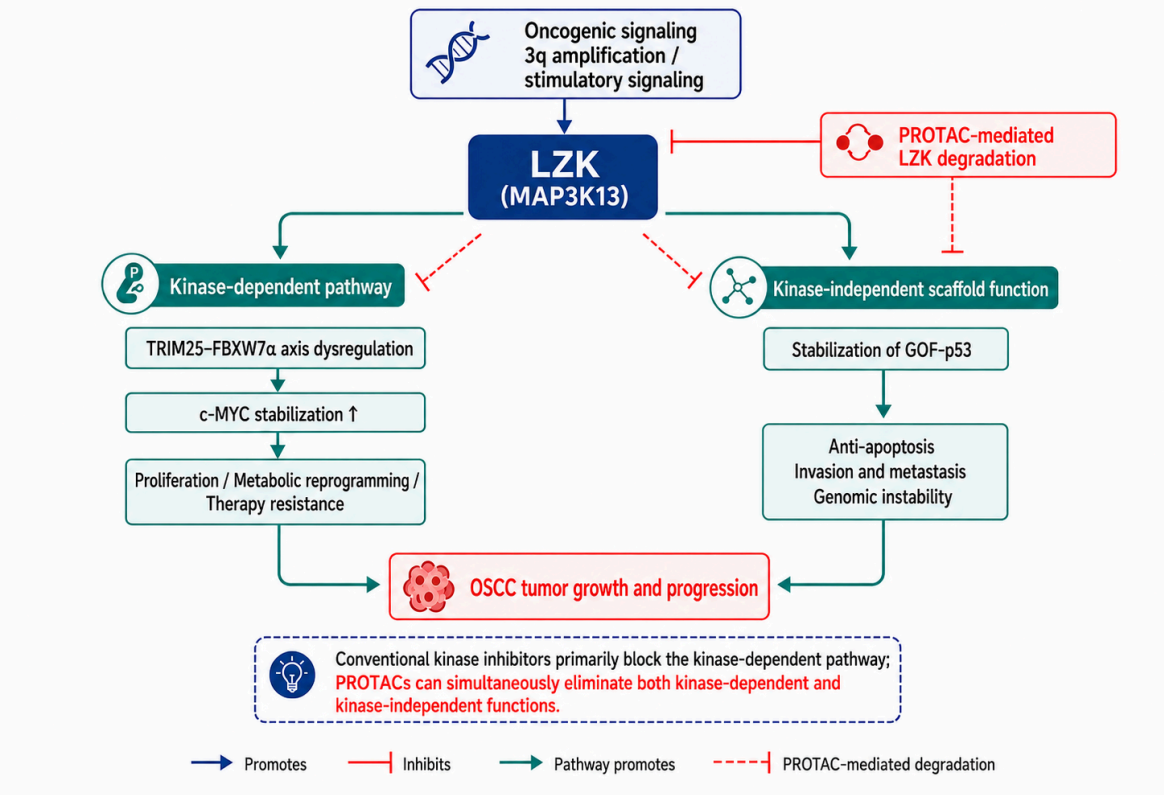


Figure 1. Dual oncogenic mechanisms of LZK and therapeutic entry point

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Leucine zipper-bearing kinase (LZK; gene name MAP3K13) is a serine/threonine kinase of the mixed-lineage kinase (MLK) family and participates in MAPK signaling pathways such as JNK. Previous studies have shown that LZK knockdown significantly reduces the viability and colony-forming capacity of 3q-amplified HNSCC cells, including some OSCC-derived cells, and suppresses tumor growth in xenograft models [9]. Further research indicates that LZK maintains c-MYC stability through a kinase-dependent mechanism and stabilizes GOF-p53 through a non-kinase-dependent scaffold function [10]. These findings suggest that conventional kinase inhibitors may not fully block LZK-associated oncogenic effects, whereas PROTAC-mediated protein degradation may remove both catalytic and scaffold functions. It should be noted that the key evidence currently derives mainly from HNSCC models. Although OSCC is an important subtype of HNSCC, further validation using OSCC-specific cell lines, patient-derived organoids, and animal models remains necessary.

LZK maintains c-MYC stability through kinase-dependent mechanisms and GOF-p53 stability through non-kinase-dependent scaffold functions. PROTAC-mediated LZK degradation may simultaneously interfere with both oncogenic pathways.

3. LZK-PROTAC degradation strategy: from kinase inhibition to protein degradation

3.1. From dual LZK functions to the need for protein degradation

As discussed above, the oncogenic activity of LZK does not fully depend on its kinase activity. Although conventional ATP-competitive inhibitors can block the LZK-mediated c-MYC stabilization pathway, they are theoretically unable to fully inhibit the non-kinase-dependent scaffold function of the LZK protein itself, particularly its role in maintaining GOF-p53 stability [10]. This feature suggests that LZK-directed therapeutic strategies should not remain limited to "kinase activity inhibition", but should further consider whether the LZK protein itself can be directly eliminated, thereby blocking both catalytic and non-catalytic functions.

Proteolysis-targeting chimera (PROTAC) technology is particularly relevant in this context. A PROTAC molecule usually consists of three components: a target protein ligand that recognizes and binds the protein of interest, an E3 ubiquitin ligase ligand that recruits a specific E3 ligase, and a linker connecting the two ligands. When a PROTAC simultaneously binds the target protein and the E3 ligase, it forms a target protein-PROTAC-E3 ligase ternary complex, promotes ubiquitination of the target protein, and ultimately leads to proteasome-mediated degradation [11].

Compared with traditional small-molecule inhibitors, PROTACs act through a distinct mechanism. Traditional inhibitors mainly rely on continuous occupancy of the active site of a target protein, whereas PROTACs exert their effects by inducing protein degradation. In other words, a PROTAC does not necessarily need to remain bound to the target for an extended period; after participating in one degradation cycle, it can be released and engage in subsequent cycles. Therefore, PROTACs may theoretically achieve durable target protein clearance at relatively low doses and may eliminate both enzymatic and non-enzymatic functions of the target protein [11]. This mechanism is particularly valuable for proteins such as LZK that possess both kinase activity and scaffold functions.

Nevertheless, PROTAC molecules are usually large and structurally complex, and they are often associated with translational limitations in membrane permeability and pharmacokinetics. Optimization of oral bioavailability remains an important challenge in this field [12].

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3.2. Research progress in LZK-PROTACs

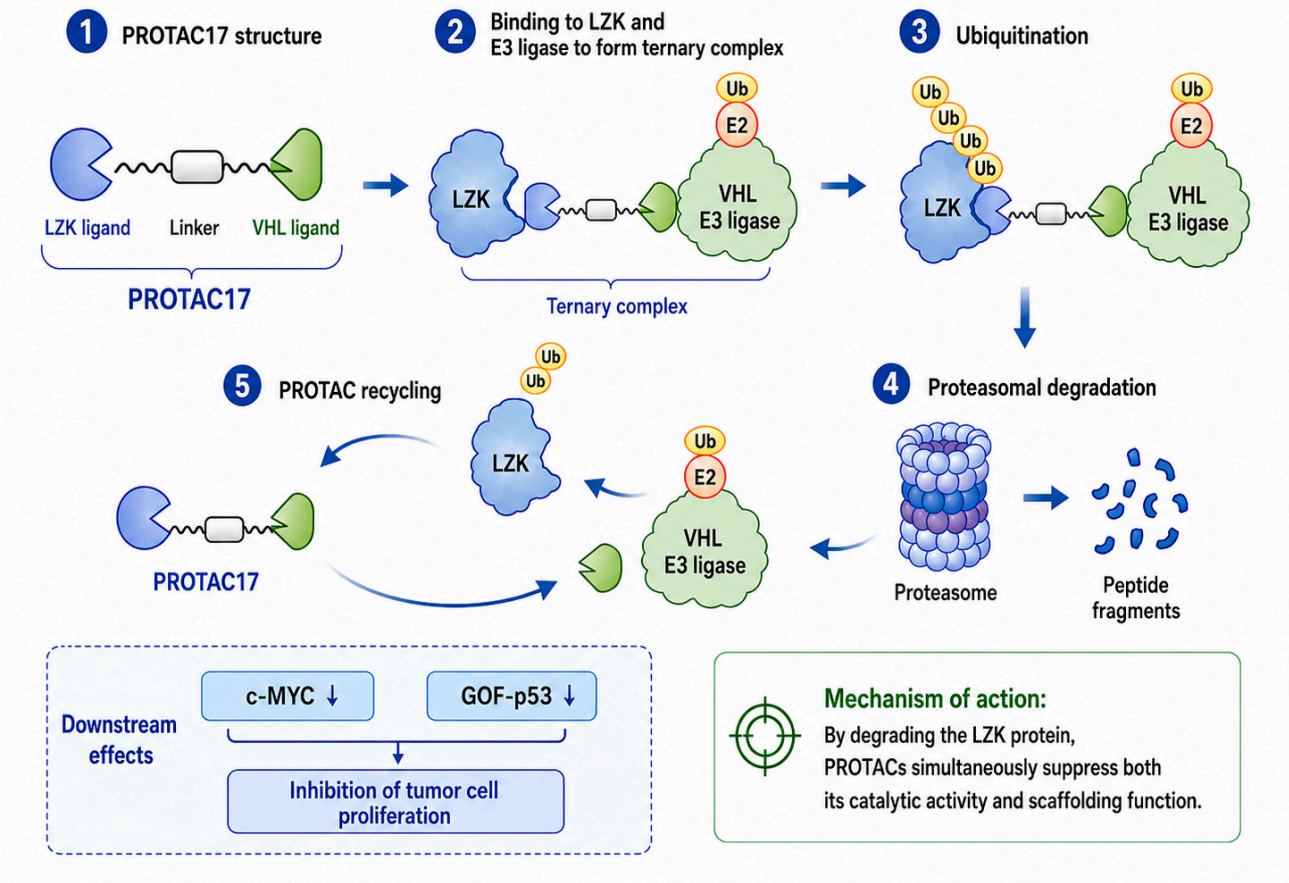


Figure 2. Mechanism of PROTAC-mediated LZK degradation

LZK-PROTAC forms a ternary complex by simultaneously binding LZK and an E3 ubiquitin ligase, induces LZK ubiquitination and proteasomal degradation, and thereby removes the LZK protein itself.

Research on LZK-directed PROTACs is mainly based on the mechanistic evidence that LZK acts as a dependency target in HNSCC. Funk et al. showed that LZK stabilizes c-MYC through a kinase-dependent mechanism and stabilizes GOF-p53 through a kinase-independent mechanism. Accordingly, the authors proposed that inducing LZK protein degradation may simultaneously reduce c-MYC and GOF-p53 levels and thereby more completely block LZK downstream oncogenic signaling than conventional kinase inhibition [10].

In early studies, researchers used the DLK/LZK inhibitor compound 21 as a targeting warhead and linked it to a VHL E3 ubiquitin ligase ligand to generate the first-generation LZK-targeting PROTAC, PROTAC-21A. This molecule induced LZK degradation and inhibited LZK-mediated JNK signaling activation and colony formation in HNSCC cells, suggesting that LZK protein degradation is mechanistically feasible [10]. However, PROTAC-21A still required relatively high concentrations, and its potency and pharmacokinetic properties required further optimization.

On this basis, Katerji et al. further optimized the LZK-targeting warhead, E3 ligase ligand, and linker structure, synthesizing and screening 27 LZK-targeting PROTAC molecules [13]. The study showed that linker length, rigidity, and spatial conformation markedly influenced LZK degradation efficiency. Among these compounds, PROTAC17 was considered a relatively promising lead

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compound. PROTAC17 consists of an LZK-targeting warhead, a VHL ligand, and a rigid cyclobutane linker. In vitro binding assays showed strong affinity for LZK, with a Kd of approximately 71 nM. In models such as CAL33, PROTAC17 induced LZK degradation at 250 nM and significantly inhibited colony formation of MAP3K13-amplified HNSCC cells at 500 nM [13].

Notably, PROTAC17 displayed a degree of selectivity. It significantly inhibited colony formation in MAP3K13-amplified CAL33 and DETROIT562 cells but had a smaller effect on BICR22 cells without MAP3K13 amplification [13]. In addition, the proteasome inhibitor MG-132 and the neddylation inhibitor MLN4924 blocked PROTAC17-induced LZK degradation, indicating that reduction of LZK protein levels mainly depends on the ubiquitin-proteasome system [13]. These findings further support LZK-PROTAC as a potential strategy for targeting MAP3K13-amplified HNSCC.

However, the experimental evidence for LZK-PROTACs currently comes mainly from HNSCC cell models, and its direct relevance to OSCC should be interpreted with caution. Although cell lines such as CAL33 have an oral origin and OSCC is an important subtype of HNSCC, OSCC is molecularly heterogeneous, and not all OSCC cases exhibit MAP3K13 amplification or LZK dependency. Therefore, before LZK-PROTACs can be advanced toward OSCC applications, the relationships among MAP3K13 amplification, LZK protein expression, TP53 mutation status, and c-MYC activation must be further clarified and validated in additional OSCC cell lines, patient-derived organoids, and animal models.

In addition, the potential effect of LZK-targeting PROTACs as adjuvant therapy for OSCC depends not only on intrinsic degradation efficiency but also on an appropriate delivery strategy. Existing reviews have suggested that local or topical delivery can increase drug exposure at the lesion site and reduce systemic exposure, thereby providing a reference for optimizing local delivery strategies for PROTAC molecules [14].

4. Dissolving microneedle-mediated local delivery: an engineering translation pathway for PROTACs in OSCC

4.1. General features of microneedle technology and advantages of dissolving microneedles

Microneedles (MNs) are minimally invasive delivery platforms composed of micron-scale needle-like structures. They can transiently penetrate epithelial or skin barriers and form local microchannels, thereby facilitating the entry of drugs, nucleic acids, proteins, peptides, or nanocarriers into tissues. According to their structure and release mechanism, microneedles are commonly classified as solid, coated, hollow, and dissolving microneedles [15]. Dissolving microneedles (DMNs) use biocompatible or degradable polymers as the matrix and encapsulate drugs or drug carriers within the needle body. After insertion into tissue, the microneedles gradually dissolve or degrade locally and release the encapsulated payload, eliminating the need for needle removal and offering advantages such as ease of use, low risk of cross-contamination, and favorable patient compliance.

Compared with conventional transdermal patches, the core advantage of microneedles lies in their ability to physically overcome epithelial barriers without relying entirely on the molecular size, lipophilicity, or passive diffusion capacity of the drug. This feature is particularly important for PROTACs. Because PROTAC molecules often fall outside the physicochemical space of classical small-molecule drugs, passive penetration alone is unlikely to achieve stable and effective local delivery. By transiently opening the barrier, microneedles can create a pathway for large or relatively

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hydrophobic molecules to enter tissues, thereby partially compensating for the insufficient delivery efficiency of PROTACs.

In terms of materials, hyaluronic acid, polyvinyl alcohol, polyvinylpyrrolidone, chitosan, gelatin, and PLGA have all been used for microneedle fabrication [15]. Hyaluronic acid has good biocompatibility and degradability and is frequently used as a dissolving microneedle matrix. Chitosan, owing to its mucoadhesive properties, film-forming ability, and biocompatibility, is also valuable in mucosal drug delivery. For the oral mucosa, which is moist, frequently mobile, and susceptible to saliva flushing, microneedle materials must achieve a balance among mechanical strength, adhesion, dissolution, drug release, and safety. Therefore, simply transferring skin microneedle designs to the oral cavity is insufficient, and material and structural optimization according to the local oral environment is required.

4.2. Existing evidence for PROTAC microneedle delivery

At present, direct studies on PROTAC microneedle delivery remain limited, but existing work provides important proof of concept. Cheng et al. reported a PROTAC microneedle patch system for antitumor therapy. In that study, the estrogen receptor α (ERα) degrader ERD308 was used as a model PROTAC and co-encapsulated with the CDK4/6 inhibitor palbociclib in pH-sensitive MPEG-PAE micelles, which were then loaded into degradable microneedle patches for local treatment of ER-positive breast cancer [16]. The design rationale was to use micelles to improve the encapsulation and stability of hydrophobic drugs and then achieve local tumor delivery and sustained release through microneedles.

The study showed that MPEG-PAE micelles underwent demicellization in a mildly acidic tumor environment, thereby promoting drug release. The microneedle patch enabled prolonged local drug retention in tumors and induced ERα protein degradation. Combined delivery of ERD308 and palbociclib produced clear tumor suppression in animal models with favorable overall safety [16]. Although the tumor type was breast cancer rather than OSCC and the target was not LZK, the study demonstrated three points relevant to the present strategy: first, PROTACs can be encapsulated in nanomicelles and loaded into microneedles; second, microneedles can enable local sustained release of PROTACs; and third, locally released PROTACs can still enter tumor cells and induce target protein degradation.

Therefore, the work by Cheng et al. does not directly prove that LZK-PROTAC microneedles can be used for OSCC, but it provides an engineering reference for the "PROTAC-nanomicelle-dissolving microneedle" delivery model. For LZK-PROTAC17, which also faces challenges related to large molecular size, hydrophobicity, and pharmacokinetic optimization, encapsulation in pH-responsive micelles followed by delivery to postoperative high-risk OSCC areas using dissolving microneedles may theoretically improve local drug concentration and reduce systemic dosing burden.

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4.3. Conceptual design of LZK-PROTAC dissolving microneedles

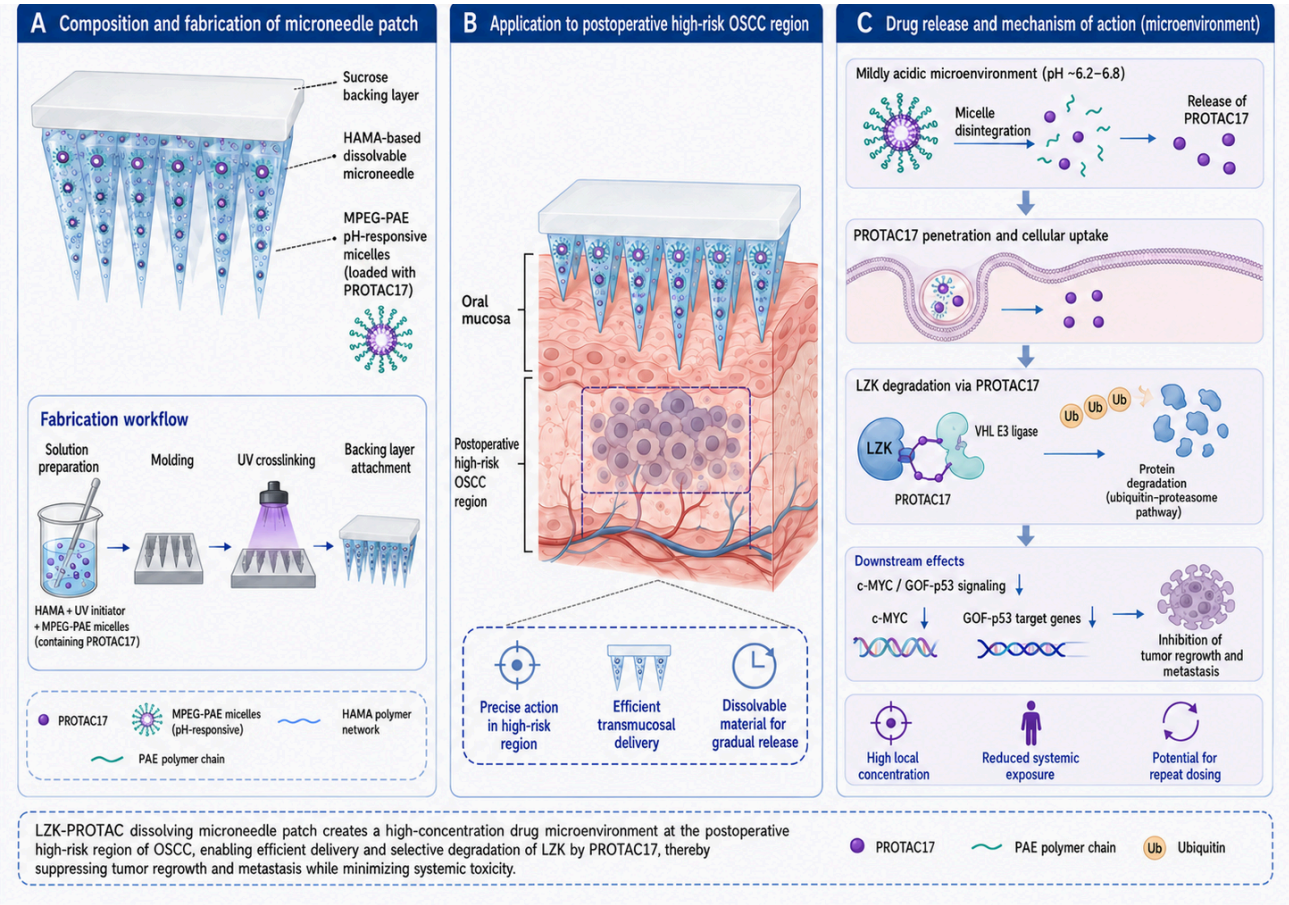


Figure 3. Schematic of local delivery of LZK-PROTAC using dissolving microneedles

pH-responsive micelles loaded with PROTAC17 are embedded in the dissolving microneedle matrix. After adhesion to the postoperative high-risk area of OSCC, the microneedles dissolve and release the drug locally, creating sustained local exposure and enabling targeted degradation.

Table 1. Key studies related to LZK-PROTACs and dissolving microneedle-mediated local delivery

Module	Representative studies	Key findings	Relevance to this review
LZK target basis	Edwards et al. [9]; Funk et al. [10]	LZK/MAP3K13 is an important dependency gene in 3q-amplified HNSCC; it stabilizes c-MYC through a kinase-dependent mechanism and GOF-p53 through a non-kinase-dependent scaffold function.	Supports LZK as a potential therapeutic target and provides the rationale that degradation may be preferable to inhibition.
LZK-PROTAC	Huang et al. [11]; Zeng et al. [12]; Katerji et al. [13]	PROTACs can degrade target proteins via the ubiquitin-proteasome system; PROTAC17 shows strong affinity for LZK and induces LZK degradation in HNSCC models.	Supports the use of LZK-PROTAC17 to indirectly modulate c-MYC and GOF-p53.

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Table 1. (continued)

Microneedle-mediated local delivery	Gioiello et al. [14]; Shivaswamy et al. [15]; Cheng et al. [16]	Dissolving microneedles enable minimally invasive local release and favorable compliance; the PROTAC-nanomicelle-microneedle combination has been validated conceptually in other tumor models.	Provides engineering reference for postoperative local delivery of LZK-PROTAC in OSCC.

Based on the available literature and the local anatomical features of OSCC, the proposed LZK-PROTAC dissolving microneedle delivery system may consist of three basic components: a drug-loaded microneedle matrix, pH-responsive nanomicelles, and a mucosa-adapted backing layer. First, HAMA or other hyaluronic acid derivatives may be selected as the main dissolving microneedle material to form a needle structure with sufficient mechanical strength and degradability. Hyaluronic acid-based materials have advantages in tissue compatibility and degradability and can serve as a scaffold for local drug release. Second, pH-sensitive micelles such as MPEG-PAE can be used to encapsulate PROTAC17, improving its aqueous dispersibility and local stability while utilizing the relatively acidic tumor microenvironment to facilitate drug release. Finally, mucoadhesive materials such as chitosan can be introduced into the microneedle base or backing layer to enhance adhesion to the oral mucosal surface and reduce detachment caused by saliva flushing and oral movements.

The expected delivery process can be summarized as follows: after the microneedle patch adheres to the postoperative high-risk area of OSCC, the needles penetrate the superficial oral mucosa and gradually dissolve, releasing pH-responsive micelles containing PROTAC17. The micelles then undergo structural changes in the local microenvironment and release PROTAC17. After uptake by residual tumor cells or high-risk epithelial cells, PROTAC17 induces the formation of a ternary complex between LZK and an E3 ubiquitin ligase, triggering LZK ubiquitination and proteasomal degradation. Following LZK degradation, kinase-dependent c-MYC stabilization and non-kinase-dependent GOF-p53 stabilization may theoretically be attenuated simultaneously, thereby suppressing the proliferative potential of microscopic residual lesions.

It should be emphasized that this design remains a literature-based strategic concept rather than an experimentally validated therapeutic regimen. Its rationale is based on three lines of evidence: first, LZK has therapeutic potential in MAP3K13-amplified HNSCC [9, 10]; second, LZK-PROTAC17 has been shown to induce LZK degradation and inhibit cell proliferation in HNSCC cell models [13]; and third, PROTAC microneedle delivery has been validated conceptually in other tumor models [16]. Whether LZK-PROTAC microneedles can achieve stable adhesion, effective drug release, sufficient cellular uptake, and safe repeated dosing in the postoperative local environment of OSCC still requires further experimental validation.

5. Conclusions and perspectives

LZK has both kinase-dependent and non-kinase-dependent scaffold functions and represents a potential upstream regulatory node linking c-MYC and GOF-p53. Compared with conventional kinase inhibitors, PROTAC-mediated LZK degradation is more likely to simultaneously block its catalytic and non-catalytic functions, providing a new approach for indirectly targeting c-MYC and GOF-p53, which are difficult to inhibit directly. Dissolving microneedle-mediated local delivery is compatible with the superficial location of OSCC lesions and the accessibility of postoperative high-risk areas, and may increase local drug exposure while reducing systemic toxicity. However, the current evidence is mainly derived from HNSCC cell models and microneedle delivery studies in

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other tumor types. Further validation in OSCC cell lines, patient-derived organoids, and animal models is needed. Future studies should focus on patient subgroup selection, PROTAC delivery efficiency, mucosal compatibility of microneedles, local safety, and the feasibility of repeated dosing, thereby providing a basis for translating this strategy into postoperative adjuvant therapy.

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