Molecular Role of CLIC1 in Oral Cancer: From Ion Channel Dynamics to Tumorigenesis

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Abstract

Oral squamous cell carcinoma (OSCC) remains a globally prevalent malignancy with limited effective biomarkers and molecular targets for early detection and therapy. The chloride intracellular channel 1 (CLIC1), a redox-sensitive protein with dual localization in cytosolic and membrane-bound forms, has emerged as a key regulator of ion homeostasis and tumorigenesis. CLIC1 translocates from cytosol to the plasma membrane under oxidative conditions, modulating chloride flux and influencing intracellular ROS balance, which in turn affects cell survival and proliferation. Functionally, CLIC1 overexpression in OSCC correlates with enhanced cell proliferation, invasion, angiogenesis, and lymphatic metastasis, whereas its inhibition promotes apoptosis and chemosensitivity. Mechanistically, CLIC1 interacts with oncogenic signaling pathways, including NF-κB, PI3K/Akt, and p53, creating a feedback loop where ROS-mediated redox shifts drive ERK/MAPK activation and integrin signaling. Network pharmacology and protein–protein interaction analyses reveal that the CLIC1 interactome converges on genes governing cell cycle control, epithelial–mesenchymal transition, and mitochondrial metabolism, linking its channel dynamics to aggressive tumor phenotypes. Given its consistent overexpression across tumor grades and its association with poor prognosis, CLIC1 represents a promising theranostic candidate in OSCC. Targeting its redox-regulated ion channel function or downstream effectors may offer new strategies for precision intervention and biomarker-driven therapy in oral cancer management.

Keywords: CLIC1, Oral squamous cell carcinoma (OSCC), redox, ion channels, signaling

1. Introduction

Oral squamous cell carcinoma (OSCC) represents nearly 90% of oral malignancies and remains a major public health burden worldwide, particularly in South and Southeast Asia. According to global projections, the incidence of OSCC is expected to rise by at least 40% by 2040, driven by persistent exposure to tobacco, alcohol, betel quid chewing, and human papillomavirus infection. Despite advances in surgery, radiation, and systemic therapy, the 5-year survival rate has plateaued below 60%, underscoring the urgent need for molecularly guided diagnostics and targeted interventions. Molecularly, OSCC is a heterogeneous disease marked by genomic instability, widespread mutations in TP53, PIK3CA, and CDKN2A, and epigenetic dysregulation of tumor suppressor pathways. Aberrant activation of EGFR, TGF-β, and Wnt signaling pathways drives epithelial–mesenchymal transition (EMT), invasion, and metastasis.[1,2,3,4,5,6]

Ion channels, long regarded as mere electrical conduits, have now been recognized as integral regulators of tumor biology, giving rise to the concept of oncochannelopathies. These channels, encompassing voltage-gated, ligand-gated, and mechanosensitive classes, govern ionic homeostasis, membrane potential, and signal transduction. Dysregulation of channel proteins can sustain cancer hallmarksuncontrolled proliferation, inhibition of apoptosis, metastatic migration, and angiogenesisby coupling extracellular stimuli to intracellular oncogenic signaling. For instance, aberrant calcium and chloride fluxes have been shown to influence the activation of MAPK and PI3K/Akt pathways, while potassium channels modulate cellular volume and apoptotic signaling. Thus, ion channel

dysfunctions form a nexus connecting membrane excitability with oncogenic transformation, redefining tumors as "electrically active" biological systems.[7,8]

Within this context, the chloride intracellular channel protein 1 (CLIC1) exemplifies a prototypical oncochannel. Belonging to the conserved CLIC family, CLIC1 is unique due to its structural plasticityit can exist as a soluble cytoplasmic enzyme or switch to a membrane-embedded ion channel under oxidative or acidic conditions. Structurally, CLIC1 comprises two domains: an N-terminal thioredoxin-like domain with a redox-sensitive cysteine (Cys24) critical for its conformational transition, and a C-terminal all-helical domain that supports membrane insertion. Phylogenetically, CLIC proteins are conserved across metazoans and function in diverse physiological processes such as endosomal acidification, mitochondrial ROS regulation, and cell volume control. The redox-dependent conversion from soluble to membrane-bound form enables CLIC1 to act as both a sensor and effector of oxidative stress, thus integrating cellular metabolic states with ion signaling.[9,10,11]

In normal physiology, CLIC1 participates in processes such as endothelial permeability, macrophage activation, and maintenance of intracellular chloride gradients. However, in cancer, this adaptive behavior becomes pathologic. Elevated ROS in the tumor microenvironment induces oxidative modifications within CLIC1, promoting its translocation to the plasma membrane where it enhances chloride conductance, modulates intracellular pH, and activates downstream pro-survival kinases. In OSCC and other epithelial cancers, overexpression of CLIC1 is associated with increased migration, invasion, and angiogenesis, partly mediated by integrin-linked MAPK/ERK signaling.[9,12]

Given this evidence, the present review aims to elucidate the molecular and signaling mechanisms of CLIC1 in oral squamous cell carcinoma, bridging insights from ion channel biology, redox chemistry, and tumorigenic signaling. The objective is to construct an integrative mechanistic model describing how CLIC1's redox-sensitive ion channel dynamics orchestrate ROS modulation, apoptosis evasion, and metastatic behavior through pathways such as p53, NF-κB, and PI3K/Akt. Furthermore, the review will explore network pharmacology perspectives on the CLIC1 interactome to identify core targets and pathways linked to oncogenic transformation. Understanding CLIC1's pleiotropic roles may ultimately refine its value as a biomarker and unveil new therapeutic strategies for OSCC precision medicine.[10,11]

2. CLIC1 Structural Biology and Localization Dynamics

2.1 Protein Architecture

Chloride Intracellular Channel 1 (CLIC1) is a structurally unique and functionally versatile *metamorphic protein*, capable of existing in two distinct states: a soluble cytosolic form and a membrane-inserted ion channel form. This ability to reversibly transition between conformations underlies its role as both a redox sensor and an effector molecule, finely tuned to respond to the oxidative and ionic milieu of the cell. CLIC1 is a 241-amino-acid protein (~27 kDa), encoded on chromosome 6p21, and belongs to the highly conserved glutathione S-transferase (GST) superfamily, particularly sharing features with the GST-omega class.[13,14,15]

The architecture of soluble CLIC1 is composed of two major domains: an N-terminal thioredoxin-like domain and a C-terminal all-α-helical domain. The thioredoxin-like N-domain contains four β-strands flanked by three α-helices, forming a monothiol active site motif Cys-Pro-Phe-Ser, in which the cysteine residue at position 24 (Cys24) plays a central redox-sensitive role. The C-terminal domain, comprising helices h4–h9, is predominantly helical and contributes to membrane interaction and structural stability. Three cysteine residues (Cys24, Cys178, and Cys223) are conserved among vertebrate CLIC1 proteins, of which Cys24 lies proximal to the eventual pore region upon membrane insertion. Mutagenesis studies have shown that oxidation of Cys24 forms intramolecular disulfide bridges that alter conformational flexibility, facilitating the exposure of hydrophobic residues necessary for bilayer interaction.[15,16,17,18]

CLIC1 harbors a GST-like fold, conferring dual identity as an oxidoreductase enzyme and an ion channel. X-ray crystallography and NMR analyses revealed a latent glutathione (GSH)-binding site within the thioredoxin domain, signifying that the soluble form possesses enzymatic activity that may regulate its ion channel behavior. This duality defines CLIC1 as a "moonlighting" proteinits enzymatic oxidation-reduction function can coexist with or modulate its conductance properties. Structural dynamics studies using SAXS and NMR have confirmed that the soluble form exists in equilibrium between compact and partially extended conformations, underscoring its intrinsic flexibility.[13,14,15]

The membrane insertion mechanism of CLIC1 represents one of the most intriguing transformations known among intracellular ion channels. Biophysical studies and cryo-electron microscopy have demonstrated that CLIC1 can spontaneously insert into lipid bilayers without the need for chaperones or ATP hydrolysisa feature that distinguishes it from canonical membrane channels. Recent mechanistic models propose a Zn^{2+}-triggered two-step transition, in which zinc binding induces structural rearrangements and oligomerization (dimer to tetramer), priming CLIC1 for insertion into membranes. pH-sensitive gating follows, activating chloride efflux in acidic environments such as endosomes and tumor microdomains. Residues R29 and W35 within the putative transmembrane (TM) segment are pivotal for this insertion process, modulating membrane affinity and oligomeric pore assembly.[14,17,19,20]

2.2 Subcellular Localization and Functional Switching

CLIC1 exhibits an exceptional pattern of subcellular localization, dynamically partitioning between the cytoplasm, plasma membrane, mitochondria, endoplasmic reticulum, and nucleus depending on cellular redox status and environmental stimuli. In resting cells, CLIC1 predominantly exists as a soluble monomer or dimer in the cytosol, performing glutaredoxin-like enzymatic activities involved in ROS detoxification and S-glutathionylation processes. Upon oxidative or acidic challenge, such as during hypoxia or inflammation, CLIC1 undergoes conformational extension and translocates to target membranes, including the plasma membrane and mitochondrial inner membrane, where it assembles into chloride-permeable channels.[9,11,13,17,19]

At the plasma membrane, CLIC1 contributes to chloride flux regulation, membrane potential modulation, and cell volume controlfactors critical for proliferation and migration. In mitochondria, its localization is linked to oxidative phosphorylation and metabolic adaptation; CLIC1 facilitates ROS signaling by sustaining mitochondrial membrane potential and regulating apoptosis thresholds. Nuclear localization, while less common, has been observed in highly proliferative cells and may involve redox-dependent nuclear translocation motifs associated with transcriptional stress responses.[9,11,21,22]

The redox control of localization and oligomerization forms the basis of CLIC1's functional versatility. The oxidation state of Cys24 determines whether CLIC1 remains cytosolic or inserts into membranes. Under mild oxidative stress, cysteine oxidation triggers conformational loosening and hydrophobic exposure, favoring dimerization and subsequent insertion into lipophilic membranes. Severe oxidative states, however, can lead to disulfide over-formation, impairing channel conductance and leading to mislocalization. Interestingly, the oligomerization processtransitioning from monomers to dimers and tetramersis not random but guided by interdomain rearrangements stabilized by Zn^{2+} coordination. These multimeric assemblies form the functional chloride pores, whose conductance can be modulated by pH, lipid charge, and ROS flux.[14,17,19]

In the tumor microenvironment (TME), these redox and localization dynamics are particularly relevant. Cancer cells display elevated ROS levels and local acidosis, both of which activate CLIC1 insertion and chloride flux. Functional CLIC1 channels amplify oxidative signaling by promoting sustained NADPH oxidase activity and calcium pathway crosstalk, thereby supporting proliferation, angiogenesis, and migration. Furthermore, altered dimer-to-monomer ratios have been reported in cancer stem cells, where oxidation-mediated dimeric CLIC1 enhances self-renewal and therapy resistance phenotypes. The redox-sensitive switch between soluble and membrane-bound CLIC1 thus embodies a molecular adaptation to oncogenic stress, enabling cells to survive under fluctuating oxidative environments.[21,22]

3. Redox Regulation and ROS-Dependent Signaling

3.1 CLIC1 and Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS) act as crucial secondary messengers in cellular signaling but also contribute to oxidative stress when their generation exceeds antioxidant capacity. CLIC1 stands out as both a sensor and effector in oxidative stress responses, enabling cells to couple redox fluctuations with ionic signaling. Structurally, CLIC1's redox sensitivity arises from the cysteine thiol at position 24 (Cys24), which undergoes reversible oxidation–reduction reactions that regulate the conformational shift between its soluble and membrane-inserted forms. Under oxidative stress, CLIC1 translocates to the plasma membrane or mitochondrial membrane, where it forms active chloride channels that modulate intracellular chloride flux and redox homeostasis.[23,25]

Functionally, CLIC1 operates in a feed-forward ROS loop. Activated CLIC1 channels facilitate charge compensation during NADPH oxidase (NOX) activation, thereby sustaining superoxide generation. This mechanism, initially characterized in microglial cells, is highly conserved and repurposed in cancer cells, including OSCC, to maintain elevated ROS signaling that supports proliferation and invasion. Elevated ROS levels promote further oxidation of CLIC1, enhancing its membrane localizationa self-amplifying cycle that couples ion conductance with redox flux. Consequently, upregulation of CLIC1 correlates with oxidative stress adaptation and tumor progression, while inhibition or silencing of CLIC1 impairs ROS production and enhances oxidative cytotoxicity.[12,21,23,24,25]

In OSCC, CLIC1 expression is markedly increased and positively correlates with tumor grade, invasion depth, and vascularity, reflecting the oxidative burden within the tumor microenvironment. Mechanistically, this is mediated through the ROS/ERK and ROS/p38-MAPK signaling axes, where CLIC1 enhances phosphorylation of ERK and p38, thereby promoting epithelial–mesenchymal transition and cell migration. Conversely, CLIC1 depletion reduces MAPK activity, leading to apoptosis, mitochondrial depolarization, and cell-cycle arrest. This interplay suggests a model where CLIC1 senses oxidative perturbations, activates NOX via chloride efflux, and perpetuates ROS-dependent oncogenic signaling through MAPK and PI3K/Akt cascades. Thus, CLIC1 functions as a "redox rheostat" allowing oral cancer cells to finely balance proliferation and oxidative stress tolerance.[21,24,25]

Experimental inhibition of CLIC1 using IAA-94 or gene silencing attenuates cellular ROS accumulation and enhances antioxidant enzyme activity, specifically superoxide dismutase (SOD), while decreasing lipid peroxidation products such as malondialdehyde (MDA). These data underscore the role of CLIC1 in maintaining the pro-oxidant state characteristic of OSCC and other epithelial cancers. Collectively, CLIC1 integrates redox and ionic homeostasis to sustain a metabolic phenotype conducive to growth, invasion, and survival under oxidative duress.[21,23,25]

3.2 Impact on Apoptosis and Cell Cycle

Beyond its role in ROS regulation, CLIC1 profoundly influences apoptotic resistance and cell-cycle progressiontwo hallmarks of cancer survival. CLIC1 localizes to mitochondria during oxidative stress, where its activity modulates the mitochondrial membrane potential ($\Delta\Psi m$) and redox-dependent apoptotic pathways. Excessive CLIC1 activation enhances mitochondrial ROS production and stabilizes $\Delta\Psi m$, thus delaying cytochrome c release and subsequent caspase cascade activation. Conversely, suppression of CLIC1 increases mitochondrial permeability transition, leading to activation of intrinsic apoptosis via caspase-3 and caspase-9. In OSCC models, knockdown of CLIC1 significantly upregulates caspase expression and reduces proliferation, while overexpression confers resistance to cisplatin-induced apoptosis.[12,26,27]

Recent transcriptomic studies reveal that CLIC1 modulates the balance between pro- and anti-apoptotic proteins through the Bcl-2 family network. Gain-of-function CLIC1 upregulates Bax and downregulates Bcl-2, tipping cells toward survival equilibrium in high-ROS conditions. Moreover, its regulatory cross-talk with the Nrf2/HO-1 antioxidant pathway suggests CLIC1 suppresses cellular antioxidant defense mechanisms, reinforcing oxidative stress conditions favorable to proliferation. Such interactions likely contribute to apoptosis evasion in OSCC, where ROS signaling and CLIC1 overexpression act synergistically to promote cell survival.[26]

In addition to apoptosis regulation, CLIC1 actively participates in cell-cycle control, particularly at the G1/S checkpoint. Oxidative signaling via CLIC1 activation enhances expression of cyclins (Cyclin D1, Cyclin E) and cyclin-dependent kinases (CDK2, CDK4), thereby facilitating S-phase entry. Parallel activation of the PI3K/Akt pathway promotes phosphorylation and inhibition of p21 and p27, classic CDK inhibitors, allowing unchecked proliferation. Importantly, CLIC1-driven redox imbalance affects transcription factors such as NF-κB and c-Myc, which govern the expression of G1–S progression genes. Thus, through redox-controlled kinase signaling and transcriptional reprogramming, CLIC1 integrates oxidative metabolism with cell-cycle acceleration.[28,29]

The cross-talk between redox status and proliferative signaling mediated by CLIC1 establishes a self-reinforcing feedback network: enhanced ROS promotes CLIC1 activation; active CLIC1 drives chloride conductance and NOX activity; and the resulting ROS burst activates ERK, PI3K/Akt, and NF-κB pathways that stimulate cyclin expression and suppress apoptosis checkpoint proteins. This loop not only fosters tumor growth but also enables dynamic adaptation to therapeutic stresscontributing to chemoresistance and relapse risk in OSCC.[21,24,25]

Taken together, the redox and cell-cycle regulatory functions of CLIC1 underscore its dual nature as both a modulator of oxidative metabolism and a gatekeeper of cell fate decisions. Its ability to synchronize ROS production with

proliferative and anti-apoptotic signaling pathways positions it as a pivotal molecular switch in oral carcinogenesis. Therefore, targeted disruption of the CLIC1-ROS axis presents an attractive therapeutic opportunity to restore redox balance, induce apoptosis, and enhance the responsiveness of OSCC cells to chemotherapy.[12,21,25,26]

4. Interaction with Major Oncogenic Pathways

4.1 CLIC1–p53 Axis

The chloride intracellular channel 1 (CLIC1) plays a key modulatory role in the p53-mediated redox–transcriptional network that governs cell survival and stress responses in oral squamous cell carcinoma (OSCC). Classical p53 activation is triggered by genotoxic or oxidative stress, leading to transcription of genes involved in apoptosis, DNA repair, and metabolic regulation. CLIC1, through its redox-sensitive cysteine residue (Cys24), functions at the intersection of redox signaling and ion flux, thereby modulating p53 activity via oxidative cues. Elevated CLIC1 in OSCC leads to sustained ROS generation through NADPH oxidase activation and mitochondrial dysfunction, creating an oxidative environment that shifts p53 dynamics from transient activation to chronic suppression. Under low to moderate ROS, CLIC1-driven redox flux promotes p53 stabilization through mild oxidative modification at critical cysteine residues (Cys124, Cys277), enhancing p53's transcriptional role in antioxidant defense and DNA repair. However, chronic CLIC1 activation induces high ROS, resulting in inhibitory post-translational modifications, such as S-glutathionylation or S-nitrosylation, which reduce p53's DNA-binding activity and tilt the balance toward tumor survival.[21,30,31]

Emerging experimental evidence supports a bidirectional relationship between p53 and CLIC1. In hepatocellular carcinoma and other epithelial cancers, TP53 has been shown to transcriptionally regulate CLIC1 expression via direct promoter binding, indicating CLIC1 as a downstream effector of the p53 pathway. Chromatin immunoprecipitation assays confirmed TP53 occupancy in the CLIC1 promoter region, where TP53 knockdown markedly downregulated CLIC1 transcript and protein levels. Conversely, elevated ROS flux arising from CLIC1 activation suppresses wild-type p53 activity and enhances mutant p53 stability, suggesting a feedback loop that converts transient stress adaptation into persistent oncogenic signaling. This redox–p53 feedback mechanism likely facilitates OSCC progression by impeding apoptosis while maintaining metabolic viability under oxidative microenvironments. In such conditions, CLIC1 acts as both a substrate and regulator of p53-mediated transcriptional networks, influencing decisions between survival and apoptosis.[32,33]

The CLIC1–p53 axis represents a redox-tuned regulatory interface where chloride channel activity influences p53 transcriptional outcomes. In OSCC, where oxidative stress and genomic instability coexist, dysregulated CLIC1 expression may impair p53-dependent tumor suppression while reinforcing redox adaptation mechanisms. Therapeutically, CLIC1 inhibition could restore p53's antioxidant and pro-apoptotic function, making this axis a compelling target for redox-based intervention strategies.[30,32,33]

4.2 CLIC1–NF-κB Pathway

The NF-κB pathway is a master regulator of inflammation-linked tumorigenesis, integrating cytokine signaling, oxidative stress, and cell survival responses across multiple cancer models, including OSCC. CLIC1 has emerged as a pivotal component connecting ROS signaling to NF-κB activation, creating a self-sustaining inflammatory loop that fuels malignant progression. Under oxidative conditions, CLIC1 inserts into membranes and facilitates chloride efflux, maintaining ionic balance during sustained ROS generation. This redox imbalance activates IκB kinase (IKK), which phosphorylates and degrades IκBα, releasing NF-κB dimers (p65/p50) to translocate into the nucleus. Immunoprecipitation data confirm that CLIC1 physically interacts with the IKK complex, potentiating its activity and promoting downstream transcription of inflammatory cytokines such as IL-6 and TNF-α.[34,35,36]

In OSCC and other epithelial tumors, the CLIC1–ROS–NF-κB signaling loop underlies chronic inflammation, matrix remodeling, and therapy resistance. Activation of NF-κB upregulates COX-2, MMP9, and VEGF, driving angiogenesis and invasive potential. High intracellular ROS sustained by CLIC1 contributes to the nuclear persistence of NF-κB, prolonging the transcription of pro-survival genes such as Bcl-2 and XIAP. Conversely, CLIC1 knockdown suppresses NF-κB p65 phosphorylation and nuclear translocation, leading to decreased IL-6 secretion and enhanced chemosensitivity. Moreover, CLIC1 influences macrophage polarization and immune microenvironment reprogramming by amplifying tumor-associated macrophage (TAM) recruitment through NF-κB-mediated cytokine

release. This inflammatory amplification not only promotes angiogenesis but also contributes to immune escape within the OSCC microenvironment.[12,24,34,35,36]

Thus, CLIC1 acts as a redox-ionic modulator of NF-κB signaling, coupling oxidative membrane events to transcriptional inflammation. Its inhibition abolishes feedback reinforcement between ROS and NF-κB, thereby reducing chronic inflammation and tumor aggressiveness. Given that NF-κB inhibition sensitizes OSCC cells to radiation and chemotherapy, dual targeting of CLIC1 and NF-κB may represent a synergistic approach to attenuate both oxidative and inflammatory drivers of malignancy.[35,36]

4.3 CLIC1–PI3K/Akt Signaling

The PI3K/Akt/mTOR axis is among the most frequently dysregulated oncogenic cascades in OSCC and contributes to proliferation, metabolic adaptation, and therapy resistance. CLIC1 directly and indirectly modulates this pathway at multiple nodes through ROS-dependent and integrin-linked mechanisms. Overexpression of CLIC1 promotes Akt phosphorylation, leading to enhanced activity of downstream mTOR and p70S6 kinase, which regulate protein synthesis and cell growth. Mechanistic studies indicate that CLIC1-mediated chloride flux and ROS accumulation facilitate PI3K activation via oxidation of PTEN, a negative regulator of PI3K signaling. This oxidative inactivation of PTEN increases PIP3 accumulation at the membrane, thereby amplifying Akt signaling.[21,24,37]

In OSCC models, upregulated CLIC1 correlates with increased phosphorylation of Akt and mTOR complex 1 components, driving anabolic metabolism and survival under stress. Conversely, CLIC1 silencing restores PTEN activity, decreases Akt activation, and induces G1 arrest due to reduced cyclin D1/CDK4 signaling. The redox-enriched tumor microenvironment augments CLIC1's effect on PI3K through nitric oxide and superoxide cross-talk, which further stabilizes the active Akt conformation. Additionally, integrin-linked CLIC1 signaling promotes adhesion and migration through FAK and PI3K coactivation, coupling cytoskeletal dynamics with oncogenic growth pathways. As a result, CLIC1 functions upstream as a redox amplifier of the PI3K/Akt cascade.[12,24,37]

Beyond PI3K and Akt, CLIC1 influences mTOR signaling at the translational level. Elevated ROS linked to membrane-localized CLIC1 activates mTORC1, enhancing eIF4E-mediated translation of proliferation-associated transcripts, including MYC and HIF-1α. Inhibition of CLIC1 suppresses this translational upsurge, decreases ATP production, and heightens sensitivity to mTOR inhibitors, underscoring its role in metabolic resilience. Furthermore, evidence from esophageal and lung carcinoma models demonstrates that CLIC1-dependent mTOR activation operates in parallel with NF-κB signaling, providing a coordinated pro-survival network.[21,37]

This intricate CLIC1–ROS–PI3K/Akt–mTOR circuit exemplifies a layered regulatory system integrating redox, ionic, and metabolic signals to support OSCC persistence and therapy resistance. By interfacing with both upstream oxidative cues and downstream translational machinery, CLIC1 bridges bioenergetic control with oncogenic signaling. Targeting this convergence may yield improved outcomes by simultaneously impairing redox balance, PI3K/Akt signaling, and mTOR-driven growth. Therefore, CLIC1 represents not merely a passive redox effector but a functional conductor orchestrating adaptive survival through the PI3K/Akt/mTOR network in oral carcinogenesis.[37]

5. Systems Biology and Network Pharmacology Insights

5.1 Bioinformatics Workflow

To elucidate the systemic role of CLIC1 in oral squamous cell carcinoma (OSCC), bioinformatics-based network pharmacology and systems biology methodologies were employed, focusing on high-confidence protein–protein interaction (PPI) networks and pathway enrichment analysis. The workflow commenced with data mining of CLIC1-associated genes and proteins from curated databases such as STRING (Search Tool for the Retrieval of Interacting Genes/Proteins), which integrates known and predicted PPIs based on experimental data, co-expression, and literature mining. Using STRING, the immediate and secondary interactors of CLIC1 were identified, providing a comprehensive interactome relevant to OSCC tumor biology.[38,39]

Next, the PPI network data was imported into Cytoscape, an open-source platform for visualizing complex networks. Advanced Cytoscape plugins such as ClueGO and MCODE were utilized to perform functional enrichment analysis and molecular complex detection, respectively. This enabled clustering of proteins into subnetworks based on

shared biological processes and pathways. Annotation of clusters was performed using databases such as KEGG (Kyoto Encyclopedia of Genes and Genomes) to map involved signaling cascades, including oxidative stress response, apoptosis regulation, and inflammatory pathways.

For OSCC specificity, gene expression profiles and differential gene expression datasets were overlapped with the CLIC1 interactome to prioritize cancer-relevant nodes. This cross-reference underscored key proteins implicated in cancer hallmarks and redox regulation. Validation of hub gene selection was supported by integration of patient transcriptomics data, emphasizing genes with prognostic significance and established roles in OSCC progression. The network-centric approach yielded a prioritized framework to understand how CLIC1 interfaces with oncogenic modules at the systems level.[38,39,40]

5.2 Network-Level Insights

The constructed CLIC1-centered PPI network revealed several critical hub proteins forming the backbone of OSCC oncogenic signaling. These hubs included TP53, AKT1, EGFR, MYC, JUN, CDH1, CCND1, and CTNNB1, all of which are well-known regulators of cell cycle, apoptosis, proliferation, and metastasis. TP53 emerged as a dominant node, consistent with its pivotal tumor suppressor role and known regulatory interactions with CLIC1 in redox and ion signaling contexts. AKT1 and EGFR hubs underscore the integration of survival and growth factor signaling in the network, highlighting CLIC1's connection to the PI3K/Akt and MAPK/ERK axes frequently altered in OSCC.[12,33,38]

KEGG pathway enrichment of the CLIC1 interactome pinpointed clusters heavily enriched in oxidative stress response, apoptosis, and inflammatory pathways. Key oxidative stress-related proteins, such as NFE2L2 (Nrf2) and mitochondrial regulators, co-clustered with CLIC1, reinforcing its role in redox homeostasis. Apoptosis clusters featured central regulators, including caspases and Bcl-2 family members, congruent with CLIC1's function in mitochondrial and caspase-mediated cell death pathways. Inflammation-related clusters incorporated NF-κB pathway components, cytokines, and inflammasome mediators, consistent with CLIC1's role in inflammation-driven carcinogenesis and immune microenvironment modulation.[12,23,26,36]

Network topology analysis revealed that CLIC1 interacts with integrin family members (e.g., ITGαv, ITGβ1), matrix metalloproteinases (MMP2, MMP9), and adhesion molecules, connecting cytoskeletal remodeling and extracellular matrix signaling to ion channel function. These modules link CLIC1 activity to epithelial-mesenchymal transition (EMT) and invasion processes critical for OSCC metastasis. Furthermore, nodes related to cell cycle regulation, such as CCND1 (Cyclin D1) and checkpoint kinases, were embedded in the network, supporting CLIC1's influence on proliferation control.[12,38]

Visualization of the CLIC1 oncogenic network in Cytoscape depicted a densely interconnected cluster centered on CLIC1, integrating redox, survival, cell cycle, and migration pathways (Figure 1). This network highlights how CLIC1 serves as a molecular hub, orchestrating multifaceted oncogenic signals through direct PPIs and indirect pathway crosstalk. The spatial arrangement underscored distinct functional modules, such as a redox regulatory cluster dominated by NRF2 and mitochondrial proteins, an inflammatory signaling cluster clustered around NF-κB, and a proliferative module anchored by AKT1 and CCND1. Such modularity suggests that targeting CLIC1 could disrupt several tumor-promoting axes simultaneously, potentiating therapeutic efficacy.[38,39]

6. Mechanistic Integration: CLIC1 as an Oncogenic Driver in OSCC

A unified mechanistic framework positions CLIC1 as a central driver of oral squamous cell carcinoma (OSCC)integrating molecular biology and systems pharmacology to clarify its roles in redox signaling, ion channel dynamics, and oncogenic pathway activation.

Proposed Mechanism Synthesis

1. Redox-Induced Membrane Insertion:

    - In OSCC, elevated oxidative stress leads to post-translational modification of CLIC1 (notably at Cys24), triggering its translocation from the cytosol to cellular membranes (especially plasma membrane and mitochondria).

- This membrane insertion enables CLIC1 to function as an active chloride channel, contributing to ionic homeostasis and charge balance during rapid cell proliferation.[12]

2. ROS Amplification:

   - Membrane-localized CLIC1 sustains intracellular ROS production by facilitating NADPH oxidase activity (NOX) and modulating mitochondrial membrane potential. This creates a pro-oxidant tumor microenvironment that further drives malignant transformation.

   - Amplified ROS not only supports proliferation but also sets up a self-reinforcing loop boosting CLIC1 activation and sustaining redox imbalance.[12,21]

3. Activation of Oncogenic Pathways (NF-κB and PI3K–Akt):

   - CLIC1-induced ROS activate NF-κB via IKK signaling, promoting transcription of inflammatory cytokines (IL-6, TNF-α), angiogenic factors (VEGF), and anti-apoptotic proteins (Bcl-2, XIAP). This supports inflammation-driven carcinogenesis and immune evasion.

   - ROS and membrane localization of CLIC1 also facilitate PI3K/Akt pathway activation through oxidative PTEN inhibition, enhancing cellular survival, proliferation, and translation via mTOR.[12]

   - CLIC1 further interacts with integrin-linked signaling (ITGαv, ITGβ1) to promote migration, invasion, and EMT via MAPK/ERK pathway crosstalk.

4. Inhibition of p53 & Apoptosis:

   - High, sustained ROS levels and continuous oncogenic signaling through CLIC1 can suppress wild-type p53 activationeither by direct redox modification or through transcriptional repression pathways, leading to impaired DNA repair and apoptotic response.

   - Downregulation of caspase-3 and caspase-9, promoted by CLIC1, further inhibits programmed cell death and permits unchecked proliferation.[12]

   - Loss of cell cycle checkpoint control (via the cyclin–CDK system) is also a downstream effect.

5. Tumorigenic Progression:

   - These interconnected processes contribute to OSCC hallmarks: enhanced proliferation, apoptosis evasion, increased migration/invasion, angiogenesis, and chemoresistance.

   - Clinical and experimental data support this model: CLIC1 upregulation in OSCC correlates with poor prognosis, advanced stage, and increased metastatic potential.[12]

7. Therapeutic and Diagnostic Implications

Chloride Intracellular Channel 1 (CLIC1) has emerged as a promising target for therapeutic intervention and diagnostic innovation in oral squamous cell carcinoma (OSCC) due to its pivotal role in redox regulation, ion channel dynamics, and oncogenic pathway activation. This section explores the therapeutic potential of modulating CLIC1, its utility as a biomarker, and futuristic clinical strategies.

7.1 Therapeutic Potential of Targeting CLIC1

CLIC1's unique metamorphic natureas both a soluble redox enzyme and membrane-inserted chloride channeloffers multiple avenues for pharmacological targeting. Ion channel modulators that specifically inhibit the chloride conductance of membrane-localized CLIC1 can disrupt the critical ionic fluxes required for maintaining the pro-oxidant tumor microenvironment and redox-driven oncogenic signaling. Compounds such as IAA-94, a chloride channel blocker, have demonstrated efficacy in reducing CLIC1 activity, resulting in impaired OSCC cell proliferation, migration, and enhanced apoptosis in preclinical models. Importantly, the selective targeting of CLIC1

channels may minimize off-target effects associated with broader ion channel inhibitors, as CLIC1 exhibits tumor-selective overexpression and redox-activated membrane insertion compared to normal tissues.[21]

Redox-sensitive inhibitors constitute another therapeutic class aimed at disrupting the oxidative switching mechanism of CLIC1. Small molecules that modify the key cysteine residues essential for CLIC1 membrane insertion or oligomerization can prevent channel activation. Inhibitors that scavenge ROS or disrupt redox cycling, such as N-acetylcysteine (NAC) and other antioxidants, indirectly attenuate CLIC1 activity. Additionally, novel chemical probes targeting the thioredoxin-like active site within the N-terminal domain hold promise for blunting both enzymatic and channel functions of CLIC1, offering a dual mode of intervention. Given the centrality of CLIC1-mediated ROS amplification to OSCC progression, pharmacological redox modulation may synergize with existing therapies by sensitizing tumors to apoptosis and impairing metabolic adaptation.[21,25,26]

7.2 Diagnostic and Prognostic Utility of CLIC1

The robust overexpression of CLIC1 in OSCC compared to adjacent normal tissues supports its use as a diagnostic biomarker. Quantitative analyses of CLIC1 protein levels in primary tumors, lymph node metastases, and body fluids including saliva and plasma have demonstrated high sensitivity and specificity for OSCC detection. CLIC1's presence in circulating extracellular vesicles and soluble plasma fractions further offers a minimally invasive biomarker platform suitable for early screening and disease monitoring. Additionally, elevated CLIC1 expression correlates with advanced tumor stage, poor differentiation, increased angiogenesis, and metastasis, validating its prognostic significance. Longitudinal studies confirm that higher CLIC1 levels predict poorer overall survival and progression-free survival, making it a valuable marker for risk stratification and treatment planning.[12,33]

7.3 Future Therapeutic Strategies

Drug repurposing initiatives are exploring whether approved ion channel inhibitors and redox modulators could be redirected to target CLIC1-mediated pathways in OSCC. Repurposed drugs could accelerate clinical translation, reducing development time and cost. For example, blockers of chloride channels or antioxidants clinically approved for other indications are under preclinical evaluation for efficacy against CLIC1-expressing tumors.[23,31]

Leveraging nanocarrier-based drug delivery systems presents another frontier. Nanoparticles functionalized with ligands or antibodies targeting CLIC1 or associated membrane markers can facilitate tumor-specific delivery of CLIC1 inhibitors, chemotherapeutics, or siRNAs, maximizing local drug concentrations while reducing systemic toxicity. Hybrid nanosystems co-delivering ROS scavengers and ion channel blockers are conceptualized to disrupt CLIC1-driven redox-ionic crosstalk synergistically, yielding enhanced tumor suppression.[40,41]

CLIC1-targeted immunotherapy is an evolving strategy harnessing the immune system's specificity. Monoclonal antibodies directed against extracellularly exposed epitopes of membrane-inserted CLIC1 may enable targeted cytotoxicity. Coupling these antibodies to drug conjugates or CAR-T therapies targeting CLIC1-expressing tumor cells could further refine treatment precision. Such approaches may prove particularly effective in overcoming chemoresistance and in combination regimens with immune checkpoint inhibitors.[41]

Conclusion

Chloride Intracellular Channel 1 (CLIC1) emerges as a multifaceted regulator in OSCC tumorigenesis, integrating redox sensing, ion channel activity, and oncogenic signaling. Its role spans promoting proliferation, invasion, angiogenesis, and apoptosis evasion, primarily through modulating ROS balance and activating pathways such as MAPK/ERK, PI3K/Akt, and NF-κB. Elevated CLIC1 expression correlates robustly with tumor progression, poor differentiation, and adverse clinical outcomes, underscoring its relevance as a prognostic biomarker and therapeutic target. The complexity of CLIC1 function necessitates integrative experimental approaches combining molecular biology, biophysical characterization, and in vivo models with computational network pharmacology and bioinformatics to map its extensive interactome and pathway cross-talks comprehensively. Such systems-level insights will be critical to decode its context-specific roles in OSCC and to identify effective modulators with minimal off-target effects. Viewed as a central hub, CLIC1 links cellular redox control to ion transport and oncogenic signaling cascades, orchestrating malignant transformation and microenvironmental adaptation. Targeting this nexus offers a promising avenue for both mechanistic elucidation and therapeutic innovation in OSCC management. Continued

interdisciplinary research is essential to translate these insights into clinical applications that improve patient prognosis and treatment modalities.

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