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Role Of CDKN2A A Cell Cycle Regulation in diagnosis of Oral Squamous Cell Carcinoma: A Review

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ABSTRACT

Oral squamous cell carcinoma (OSCC) represents a significant global health burden, marked by high mortality and poor prognosis. It is most commonly observed in individuals who consume tobacco, particularly long-term users. The disease arises from a series of cellular and molecular changes, including alterations in gene expression that drive cancer development. Understanding and potentially reversing these genetic and epigenetic changes may aid in disease prevention and treatment.

Among the key molecular aberrations involved in OSCC pathogenesis are alterations in the *CDKN2A* gene. Located on chromosome 9p21, *CDKN2A* encodes two critical tumor suppressor proteins—p16^INK4a^ and p14^ARF^—which regulate the cell cycle and apoptosis, respectively. Loss of function in *CDKN2A* disrupts these regulatory processes, thereby promoting cancer development.

This review explores the molecular biology of *CDKN2A*, its alterations in OSCC, the associated signaling pathways, and potential therapeutic implications. Epigenetic and genetic regulation of *CDKN2A* may offer promising strategies for cancer prevention and therapy. Ongoing research into this gene and its related pathways holds the potential to deliver transformative insights, ultimately improving prognostic accuracy and treatment outcomes for OSCC patients.

Keywords: *Genes in Oral Cancer,CDKN2A in OSCC, OSCC Biomarkers,Saliva in OSCC. CDKN- cyclin dependent kinase, HNSCC- Head and Neck Squamous cell carcinoma, OSCC- Oral Squamous cell carcinoma,*

1. INTRODUCTION

Oral squamous cell carcinoma is one of the leading and second most prevalent diseases. It has been the most aggressive when it comes to its nature and progression. The oral squamous cell carcinoma is most commonly found in the tobacco consuming group especially the long term users. This disease is mainly caused by various changes happening both cellular and molecular levels. Changes or inhibition of gene expression that is responsible for such cancers could be altered, which helps in reducing and curing the diseased stated. One such biomarker is the CDKN2A, responsible for the OSCC. This biomarker has shown significant changes in treating such patients. This biomarker is a tumour suppressor gene, which could be altered in the molecular level with p16 for better results in these OSCC patients.

Oral squamous cell carcinoma (OSCC) is the most prevalent subtype of head and neck squamous cell carcinoma (HNSCC), but its incidence varies significantly based on factors such as habits, race, and geographical location [2]. OSCC accounts for more than 90% of oral cancers and is often diagnosed at advanced stages, leading to a high mortality rateIn South Asia, OSCC makes up 30% of all malignant tumors, whereas in Western countries, it accounts for only 1-4%. Despite advances in diagnostic and therapeutic modalities, OSCC's prognosis remains dismal, with a five-year survival rate below 50%, Risk factors include tobacco use, alcohol consumption, and human papillomavirus (HPV) infection OSCC develops in diverse anatomical sites, including the pharynx, larynx, sino-nasal, and oral cavity. Unravelling the molecular mechanisms involved in OSCC development and progression is essential to identify novel diagnostic biomarkers and therapeutic targets. Among these, CDKN2A has garnered significant attention as a frequently altered gene in OSCC. While OSCC has been extensively studied, its high mortality rate underscores the need for deeper molecular insights to improve patient outcomes.

The CDKN2A gene, located at chromosome 9p21, frequently undergoes genetic and epigenetic alterations in OSCC. Loss of function in CDKN2A disrupts cell cycle regulation, contributing to oncogenesis. Furthermore, CDKN2A mutations have emerged as critical determinants of patient prognosis, correlating with tumour progression, treatment resistance, and survival outcomes. The Frequencies of CDKN2A alterations were significantly higher in Older Patents than in AYA patients. It is also seen significantly higher in Primary Lesion than in metastatic lesion. Somatic alterations in OSCC involving cell cycle related genes which include CDKN2A

Cell cycle regulation is crucial in the process of tumorigenesis. In eukaryotic cells, this regulation involves the sequential activation of cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors (CDK-Is). (1) During the G1 phase, p16 (a CDK-4-I encoded by gene CDKN2A and located on chromosome 9p21.3, INK4a locus) controls the cell cycle by inhibiting the ability of cyclin D-CDK 4/6 to phosphorylate the retinoblastoma protein (pRb).

Alterations in CDKN2A/p16INK4A, a tumor suppressor gene located on chromosome 9p21, have been well-established in HNSCC. The protein encoded by CDKN2A, p16, is essential for cell cycle regulation through its interaction with the retinoblastoma (Rb) tumor suppressor. P16 inhibits cyclin-dependent kinases (CDK) 4 and 6, which are required for the phosphorylation of Rb(4,5,6). Although changes in CDKN2A are common in the early development of HNSCC, they are likely not enough by themselves to drive tumorigenesis. This is supported by the fact that CDKN2A mutations have also been observed in benign epithelial lesions with a low potential for malignant transformation. (7)

2. EPIDEMIOLOGY OF OSCC-

Oral squamous cell carcinoma shows an increased incidence and mortality rate, particularly among individuals who consume tobacco. Current estimates of age-standardized incidence and mortality are 6.6/100,000 and 3.1/100,000 in men, and 2.9/100,000 and 1.4/100,000 in women, respectively. [8] Recent studies confirm that oral cancer constitutes a significant portion of the cancer burden in certain regions of India.[9] Tobacco and alcohol are the two primary known risk factors for the development of oral cancer. [10]

Various risk factors for oral cancer include tobacco, betel quid, areca nut, alcohol, viruses, diet, family history, immune deficiency, molecular changes, tumor suppressor genes and growth regulators, as well as neovascularization.(11) In 35.7% of tumors, a nonsynonymous mutation in CDKN2A was found. Among TP53-mutated tumors across five merged subsites, 37% to 48% also exhibited CDKN2A mutations, regardless of the specific TP53 mutation category. This frequency was similarly observed in advanced-stage HNSCC or those with an occult primary.(2,7)

3. BIOGENESIS-

Biomarkers, also known as biological markers, are quantifiable indicators of a particular biological or pathological condition or observable indicators of the presence of live organisms within the body. Substances that may be secreted from the cancer cell or from the body because of oncological reaction are referred to neoplastic markers.

CDKN2A shares a strong resemblance with the well-known tumor suppressor gene, p53. It is possible that CDKN2A plays a role as crucial in regulating cell growth as p53.(12) The gene consists of three exons, including one alternatively spliced exon (E1-β). It is located on chromosome 9p21, a region known for a high frequency of loss of heterozygosity (LOH) across various tumor types. (13) The gene encodes two proteins: the INK4 family member p16 (or p16INK4a) and p14arf. Both act

as tumor suppressors by controlling the cell cycle. p16 inhibits cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), thereby activating the retinoblastoma (Rb) family of proteins, which prevent progression from the G1 phase to the S phase. (16)

This protein is part of the CDKN2 cyclin-dependent kinase inhibitor family. It binds to CDK4/6, inhibiting their kinase activity and preventing Rb phosphorylation. As a result, Rb remains bound to the transcription factor E2F1, blocking the transcription of E2F1 target genes that are essential for the G1/S transition.(16,17). Molecular cytogenetic studies have shown that melanoma and other cell lines often exhibit homozygous and heterozygous deletions in the chromosome 9p21-p22 region. (14,15) The loss of $p16^{CDKN2A}$ expression may be more closely associated with invasiveness or metastatic potential than with tumor initiation.(12)

4. THE BIOLOGY OF CDKN2A-

CDKN2A, located on chromosome 9p21.3, encodes two critical tumor suppressor proteins through alternative reading frames:

p16INK4a: A cyclin-dependent kinase inhibitor that prevents phosphorylation of the retinoblastoma (Rb) protein, halting the cell cycle in the G1 phase.

p14ARF regulates the p53 pathway by preventing MDM2-mediated degradation of p53, thereby promoting cell cycle arrest and apoptosis.

Regulation of CDKN2A Expression-

CDKN2A expression is tightly regulated by genetic, epigenetic, and transcriptional mechanisms. Aberrant methylation of the CDKN2A promoter region, homozygous deletions, and point mutations are common in various cancers, including OSCC. Furthermore, loss of heterozygosity (LOH) at 9p21 is frequently observed in oral malignancies.

5. CDKN2A ALTERATIONS IN OSCC

Genetic Alterations-

The CDKN2A locus is a hotspot for mutations and deletions in OSCC. These genetic alterations disrupt the normal cell cycle control and promote unchecked cellular proliferation. Studies have reported homozygous deletions of CDKN2A in 20-40% of OSCC cases, while point mutations occur less frequently.

Epigenetic Silencing-

Promoter hypermethylation of CDKN2A is one of the most common mechanisms leading to its inactivation in OSCC. This epigenetic alteration correlates with poor differentiation, advanced tumor stages, and worse prognoses in patients.

Loss of Heterozygosity-

LOH at 9p21, encompassing the CDKN2A locus, is a hallmark of OSCC. This event leads to a loss of tumor suppressor function and contributes to carcinogenesis. The frequency of LOH increases in high-grade and metastatic lesions, implicating its role in tumor progression.

6. PATHWAYS IMPLICATED IN CDKN2A DYSFUNCTION

Cell Cycle Dysregulation-

CDKN2A inactivation disrupts the Rb pathway by failing to inhibit CDK4/6- mediated phosphorylation of Rb, releasing E2F transcription factors and driving cell cycle progression

p53 Pathway Alterations-

Loss of p14ARF results in diminished p53 activity due to unchecked MDM2- mediated degradation. This impairment compromises apoptosis and promotes the survival of genetically unstable cells.

Interaction with Other Molecular Events-

HPV Infection: High-risk HPV oncoproteins E6 and E7 target p53 and Rb, respectively, bypassing the need for CDKN2A alterations in some OSCC cases.

Co-mutations: CDKN2A mutations often coexist with TP53, NOTCHI, or FATI mutations, exacerbating the oncogenic phenotype.

7. DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE

Biomarker Potential-

The detection of CDKN2A promoter methylation or genetic alterations in saliva, plasma, or biopsy specimens holds promise as a non-invasive diagnostic biomarker. Methylation-specific PCR (MSP) and next-generation sequencing (NGS) are

valuable tools for this purpose.

Prognostic Implications-

CDKN2A alterations correlate with worse clinical outcomes, including higher recurrence rates, lymph node metastasis, and resistance to therapy. Patients with intact CDKN2A pathways tend to have better responses to treatment and improved survival rates.

The CDKN2A gene has been found to have a high frequency of genetic and epigenetic changes in human cancer cell lines originating from different tumor types. Therefore, epigenetic/genetic regulation of CDKN2A alterations may be a promising approach to cancer prevention or treatment. The alterations in CDKN2A status vary significantly depending on the cancer type. In addition to skin cancer such as melanoma, changes of *CDKN2A* have been described in a wide spectrum of cancer types such as Burkitt's lymphoma(18), head & neck squamous cell carcinoma(19), oral cancer(20)

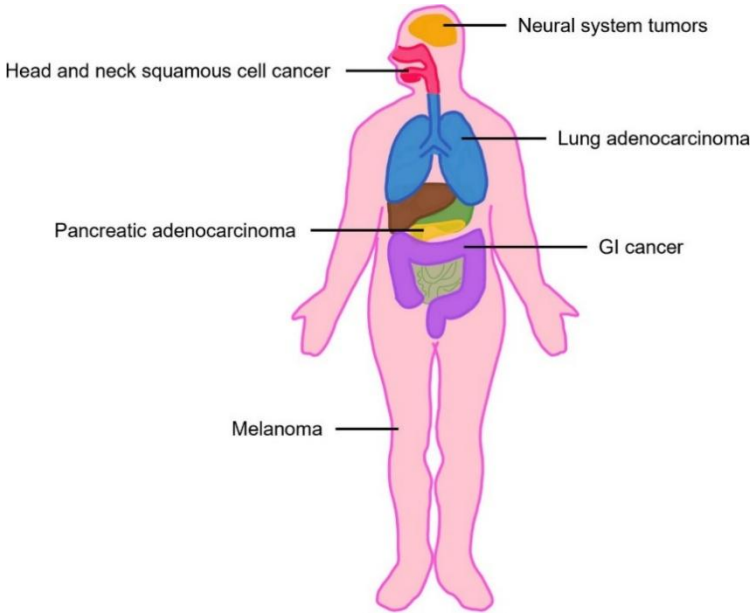


Fig. 1 *CDK2NA* germline mutation associated malignancies

Patients carrying a mutant CDKN2A gene remain asymptomatic until the normal CDKN2A gene undergoes a loss-of-function mutation, also known as loss of heterozygosity. In all HNSCC patients with a germline CDKN2A mutation, loss of heterozygosity has been observed in the tested individuals. (21-25)

8. THERAPEUTIC IMPLICATIONS-

Targeting the CDK4/6 Pathway

The development of CDK4/6 inhibitors, such as palbociclib, offers a therapeutic avenue for OSCC cases with CDKN2A loss. These inhibitors restore cell cycle control and have shown promise in preclinical and early-phase clinical trials.

Epigenetic Therapies

Reversing CDKN2A promoter methylation using demethylating agents like 5- azacytidine could restore its expression and tumor suppressor functions. Combining these agents with immunotherapy or chemotherapy may enhance their efficacy.

Synthetic Lethality Approaches

Targeting vulnerabilities induced by CDKN2A loss, such as dependency on alternative pathways like PI3K/Akt or ATR/Chk1, could provide novel therapeutic strategies.

9. CHALLENGES AND FUTURE DIRECTIONS-

Despite its significant role in OSCC, several challenges remain in translating CDKN2A research into clinical practice:

Heterogeneity in Alterations: Variability in CDKN2A alterations among patients and tumor subtypes complicates the development of universal diagnostic or therapeutic approaches.

Resistance Mechanisms: Secondary mutations or compensatory pathways can limit the efficacy of targeted therapies.

Limited Biomarker Validation: Large-scale studies are needed to validate CDKN2A as a reliable biomarker for OSCC

Future research should focus on integrating multi-omics data to better understand the interplay of CDKN2A with other molecular events.

Additionally, the exploration of combination therapies targeting CDKN2A- related pathways could offer more effective treatments.

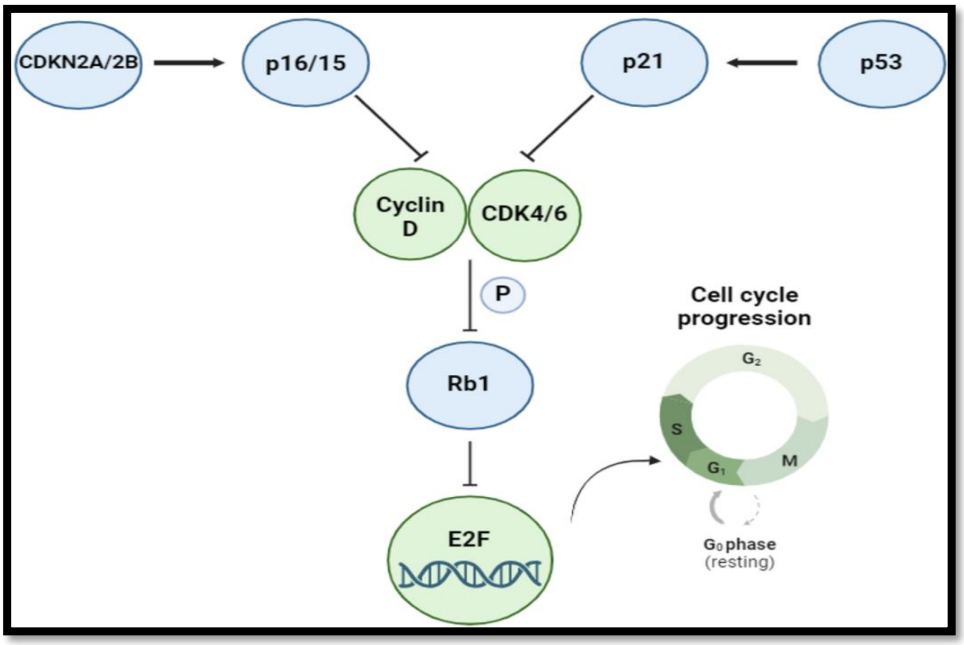
10. DISCUSSION

OSCC is a serious and aggressive cancer, and better understanding of its molecular aspects is essential for improving treatment and outcomes. The CDKN2A gene, particularly its product p16, plays a crucial role in regulating the cell cycle, and alterations in this gene are often seen in OSCC.

CDKN2a gene is an important marker in the oral squamous cell carcinoma that will help the individuals to give an early diagnosis of the diseased state. Despite advances in diagnosis and treatment, the survival rate for OSCC remains low, with fewer than 50% of patients surviving five years after diagnosis. The main risk factors for OSCC include tobacco use, alcohol consumption, and infection with Human Papillomavirus (HPV). OSCC can occur in various parts of the mouth and throat, so understanding its development at the molecular level is crucial for finding better ways to diagnose and treat it.

The CDKN2A gene, located on chromosome 9p21, is frequently altered in OSCC. When this gene is damaged, it disrupts the regulation of the cell cycle, which is a key process in cancer development. Loss of function in CDKN2A is linked to tumor growth, resistance to treatment, and poorer survival outcomes. CDKN2A changes are also more frequent in primary tumors than in metastatic tumors, which suggests they play a significant role in the early stages of OSCC.

CDKN2A plays a crucial role in the development and progression of **oral squamous cell carcinoma (OSCC)** through its encoded proteins, **p16INK4a** and **p14ARF**. These tumor suppressor proteins regulate key processes in the cell cycle and apoptosis, and alterations in the CDKN2A gene can disrupt these processes, leading to uncontrolled cell growth and cancer development. The regulation of CDKN2A expression is tightly controlled, and its disruption through mechanisms like methylation, deletions, and mutations is commonly observed in OSCC and other cancers.



The regulation of cell cycle progression by CDKN2A/2B and TP53 involves several key interactions. In the presence of mitogenic stimuli, cyclin-dependent kinases CDK4 and CDK6 phosphorylate RB1, leading to the release of E2F transcription factors from RB1/E2F complexes. These E2F factors then activate the expression of cyclin E, which drives the transition from the G1 to the S phase of the cell cycle. CDK4 and CDK6 activity is subsequently inhibited by negative cell cycle regulators such as p15 and p16 (encoded by CDKN2A and CDKN2B), along with the p53-regulated cyclin-dependent kinase inhibitor p21.[26]

The **CDKN2A** gene is a common target for genetic alterations in **oral squamous cell carcinoma (OSCC)**. These mutations and deletions interfere with the normal regulation of the cell cycle, leading to uncontrolled cell growth. One of the most common ways CDKN2A is inactivated in OSCC is through **promoter hypermethylation**. This epigenetic modification silences the gene without changing its DNA sequence. **Hypermethylation** of CDKN2A is associated with poor tumor differentiation, advanced stages of the disease, and a worse prognosis for patients. This makes CDKN2A promoter hypermethylation a potential biomarker for assessing OSCC severity.

Loss of heterozygosity (LOH) at **9p21**, where CDKN2A is located, is another hallmark of OSCC. When CDKN2A is altered, CDK4/6 can phosphorylate Rb unchecked, releasing E2F and allowing the cell cycle to progress uncontrollably. This contributes to **cellular proliferation** and **tumor growth** in OSCC, leading to cell cycle dysregulatation.

Another critical pathway affected by CDKN2A alterations is the **p53 pathway**. The protein p14ARF, encoded by CDKN2A, regulates p53 by inhibiting its degradation via **MDM2**. When p14ARF is lost, p53 is degraded unchecked, compromising its ability to induce **apoptosis** (cell death) in damaged cells.

For OSCC cases with **CDKN2A loss**, **CDK4/6 inhibitors** like **palbociclib** offer a promising therapeutic strategy. These inhibitors work by restoring control over the cell cycle, which is disrupted due to the loss of CDKN2A. Another potential therapeutic approach involves **reversing the epigenetic silencing** of CDKN2A. **Demethylating agents** like **5-azacytidine** can restore the expression of CDKN2A by reversing its promoter methylation. Another potential therapeutic approach involves reversing the epigenetic silencing of CDKN2A. Demethylating agents like 5-azacytidine can restore the expression of CDKN2A by reversing its promoter methylation. This could reinstate the gene's tumor-suppressor functions. A promising area of research is **synthetic lethality**, where tumors with CDKN2A loss are targeted through their dependence on alternative pathways. For instance, pathways like **PI3K/Akt** or **ATR/Chk1** may become essential for the survival of these tumor cells. Targeting these compensatory pathways could lead to tumor cell death without harming normal cells, providing an innovative therapeutic approach for OSCC.

11. CONCLUSION

CDKN2A serves as a central player in the molecular pathogenesis of OSCC, influencing key processes such as cell cycle regulation and apoptosis. These mutations drive tumor aggressiveness, treatment resistance, and poor survival outcomes Its alterations, whether genetic, epigenetic, or functional, contribute to tumor initiation, progression, and resistance to therapy. Advances in understanding CDKN2A biology have opened new avenues for diagnostics and therapeutics, though significant challenges remain. Continued research into this gene and its associated pathways will likely yield transformative insights, improving outcomes for patients with OSCC. It also harnessing its potential as a prognostic biomarker and therapeutic target.

Future studies should focus on integrating **multi-omics data** (e.g., genomics, proteomics, and metabolomics) to better understand how CDKN2A interacts with other molecular events in OSCC. This will provide a more comprehensive view of its role in tumor biology and open the door to novel therapeutic strategies. Additionally, **combination therapies** targeting CDKN2A-related pathways should be explored to improve treatment efficacy and overcome resistance.

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