



ROLE OF CHD1L, A POTENT ONCOGENE IN HEAD AND NECK CANCER – A SYSTEMATIC REVIEW

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Abstract

Background

The squamous and lining epithelium of the oral cavity, pharynx, and larynx is the source of head and neck squamous cell carcinomas (HNSCC). With over 700,000 new cases annually, HNSCC is the sixth most frequent cancer worldwide and accounts for between 0.5% and 1.9% of all cancer-related deaths. HNSCC is a diverse set of tumors with different anatomical sites and subsites and a range of etiological variables, such as alcohol use, smoking, and HPV infection. Although this has not been widely acknowledged, an increasing proportion of younger, low-risk individuals have been shown to exhibit a unique clinical and histological pattern linked to a worse prognosis. Intratumoral hypoxia is a common feature of solid tumors, especially skin malignancies. By initiating biological processes such as glycolysis and angiogenesis, which are critical for cancer cell survival, low oxygen tension triggers cellular responses that accelerate cancer growth. The conserved SNF2_N domain of CHD1L, a member of the SNF2-like family, is a helicase superfamily structural domain that may be essential for transcriptional regulation, DNA repair, and chromosomal integrity preservation. Thus, investigating the transcriptional regulatory network of CHD1L helps clarify its carcinogenic molecular mechanisms and may also yield new therapeutic targets for cancer treatment. CHD1L has been recognized as a new oncogene and demonstrates carcinogenic characteristics during the malignant transformation process.

Material and Methods: Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to high expression of CHD1L, a potent oncogene is associated in head and neck cancer.

Results: Five original research scientific articles dated between 2020 – 2024 pertaining to mentioned topic were highlighted.

Conclusions:

In HNSCC, CHD1L is markedly elevated and linked to poor survival rates. This implies that CHD1L could be used as a prognostic indicator and therapeutic target for HNSCC. The functional involvement of CHD1L in the onset and progression of HNSCC requires more investigation. Detailed information regarding the high expression of CHD1L, a potent oncogene is associated in head and neck cancer is discussed in this systematic review.

Key word: Head and neck cancer; squamous cell carcinoma; CHD1L; Hypoxia; oncogene; prognosis; biomarker.

INTRODUCTION:

Cancer is a genetic disease. Numerous somatic mutations, genomic rearrangements, and structural variations across different cancer types have been identified by international efforts in cancer genomics. A normal cell must undergo three to six genetic events in order to become cancerous. A typical tumor has two to eight somatic driver mutations; the remaining alterations are passenger mutations that do not confer a selective growth advantage. Important genetic alterations alter cell fate, cell survival, and genome maintenance by reprogramming normal cell growth in multiple key signaling pathways. Recently, it has been proposed to divide driver genes into "mut-driver genes" and "epi-driver genes." While epi-driver genes are expressed abnormally in tumors but are not often mutated, they are changed by changes in DNA methylation or chromatin modification that continue when the tumor cell divides. Head and neck malignancies, which are usually detected in elderly individuals with substantial alcohol and tobacco use, are gradually decreasing worldwide, partly due to a decrease in tobacco use.

Mutations that activate intracellular pathways that control cell invasion, survival, and proliferation are what propel the growth of tumors. Tumor evolution selects against mutations that oppose one another, but it retains additional variants that work in concert to boost tumor growth. Mutations in important cancer-causing oncogenes are frequently mutually exclusive, particularly if the oncogenes share a signal transduction pathway, according to data from cancer genome sequencing initiatives. The chromatin remodeling enzyme Chromodomain Helicase DNA Binding Protein 1 Like (CHD1L), often referred to as Amplified in Liver Cancer 1 (ALC1), has been identified as an oncogene linked to the pathophysiology of numerous cancer types. For patients with breast, ovarian, glioma, lung, and GI cancers, CHD1L amplification and overexpression are linked to metastatic disease, poor prognosis, and low overall survival.

Furthermore, we have identified CHD1L as a marker of low overall survival, metastasis, and poor prognosis for colorectal cancer (CRC). Different from other chromatin remodelers, CHD1L performs a wide range of cellular tasks. Poly ADP-ribose (PAR) polymerase (PARP) mediated DNA repair depends on CHD1L, and CHD1L knockdown makes tumor cells more vulnerable to chemicals that damage DNA. Through CHD1L-mediated nucleosome sliding, which reduces PARP trapping by PARP inhibitors, two recent studies confirm CHD1L as a major mechanism causing drug resistance to PARP inhibitors. When CHD1L is knocked out, BRCA1/2 mutant HR-deficient tumor cells become more susceptible to PARP inhibition, which results in cell death in vitro and decreased tumor growth with improved survival in vivo. We have identified CHD1L as an essential part of the TCF/LEF-transcription factor complex, which is implicated in the development of GI malignancies and numerous other types of cancer.

This complex is a master regulator of the epithelial-mesenchymal transition (EMT) that promotes epithelial-mesenchymal plasticity (EMP), as we and others have discovered. When overexpressed, CHD1L offers the most selective growth advantage among the CHD proteins because it greatly boosts survival and proliferation capacity compared to other CHD family members. The research of CHD1L inhibitors as possible cancer treatments has been spurred by these discoveries. CHD1L is a versatile chromatin remodeler that plays crucial roles in transcriptional control, DNA repair, embryonic development, and cellular stress responses.

Under normal physiological conditions, its activity is strictly regulated, but disruption of this regulation has been linked to an increasing variety of illnesses in humans. Rare missense mutations in CHD1L have been associated with congenital abnormalities impacting renal and reproductive development, in addition to early embryonic death seen in knockout animals. Furthermore, although these areas are still little understood, their participation in immunological signaling and chromatin remodeling raises the possibility of functions in inflammatory and stress-related illnesses.

MATERIAL AND METHODS:

"oncogene" AND "head and neck cancer" AND "CHD1L" were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024.

The result was 68 articles, out of which we selected 5 articles based in the inclusion criteria. Inclusion criteria was of case studies and scientific literature between 2020-2024. Exclusion criteria was of scientific literature irrelevant to the specific search. This systematic review was conducted to determine importance of high expression of CHD1L, a potent oncogene is associated in head and neck cancer following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL (“Oral”) AND (squamous OR carcinoma OR oncogene OR therapy OR hypoxia) AND (CHD1L)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

RESULTS: Five articles were included in this systematic review based on the selection criteria. We analysed and mentioned in the five articles reviewed. This included only relevant research articles and excluded articles pertaining to nonspecific search terms.

Table 1 – An overview

Author	Title	Journal	Outcome
Camile S Farah	Molecular landscape of head and neck cancer and implications for therapy	Farah CS. Molecular landscape of head and neck cancer and implications for therapy. <i>Annals of translational medicine</i> . 2021 May;9(10):915. doi: 10.21037/atm-20-6264	HNSCC has leveraged better therapeutic approaches to manage this group of diseases
Mei Liu, Chao Lv, Haiping Dong, Meng Zhou, Yao Yao, Huanrong Hu, Na Shen, Baoguo Liu, Guoying Miao, Yaling Liu	CHD1L accelated the progression of cutaneous squamous cell carcinoma via promoting PI3K/PD-L1 signaling pathway induced M2 polarization of TAMs	Liu M, Lv C, Dong H, Zhou M, Yao Y, Hu H, Shen N, Liu B, Miao G, Liu Y. CHD1L accelated the progression of cutaneous squamous cell carcinoma via promoting PI3K/PD-L1 signaling pathway induced M2 polarization of TAMs. <i>Scientific reports</i> . 2024 Dec 28;14(1):31231. doi: 10.1038/s41598-024-82594-2.	Under hypoxic conditions, CHD1L can promote the proliferation and migration of cutaneous squamous cell carcinoma
Muhammad Alaa Eldeen, Farag Mamdouh, Waleed K Abdulsahib, Refaat A Eid, Ahmad Alhanshani, Ayed A Shati, Youssef A Alqahtani, Mohammed A Alshehri, Mohamed Samir A Zaki, Mohamed Soltan, Ahmed Noreldin	Oncogenic Potential of Replication Factor C Subunit 4: Correlations with Tumor Progression and Assessment of Potential Inhibitors	Eldeen MA, Mamdouh F, Abdulsahib WK, Eid RA, Alhanshani AA, Shati AA, Alqahtani YA, Alshehri MA, Zaki MS, Soltan MA, Noreldin AE. Oncogenic Potential of Replication Factor C Subunit 4: Correlations with Tumor Progression and Assessment of Potential Inhibitors. <i>Pharmaceuticals (Basel, Switzerland)</i> . 2024 Jan 23;17(2):152. doi: 10.3390/ph17	RFC4's carcinogenic activities, emphasizing its potential as a prognostic biomarker and a target for anti-cancer therapy

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Kai-Li Hu, Xin Fan, Wen-Ting Hu, Hong-Li Li, Qing-Hua Tang, Xue-Hui Sun	Effect of chromodomain helicase/ATPase DNA binding protein 1-like gene on the invasion and metastasis of tongue squamous cell carcinoma CAL27 cells	Hu KL, Fan X, Hu WT, Li HL, Tang QH, Sun XH. Effect of chromodomain helicase/ATPase DNA binding protein 1-like gene on the invasion and metastasis of tongue squamous cell carcinoma CAL27 cells. Hua xi kou qiang yi xue za zhi Huaxi kouqiang yixue zazhi West China journal of stomatology. 2021 Feb 1;39(1):81-7. doi: 10.7518/hxkq.2021.01.012.	CHD1L promoted the EMT, proliferation, migration, and invasion ability of tongue squamous cell carcinoma cells
Mohamed A Soltan, Muhammad Alaa Eldeen, Refaat A Eid, Najiah M Alyamani, Leena S Alqahtani, Sarah Albogami, Ibrahim Jafri, Moon Nyeo Park, Ghadi Alsharif, Eman Fayad, Gamal Mohamed, Rihab Osman, Bonglee Kim, Mohamed Samir A Zaki	A pan-cancer analysis reveals CHD1L as a prognostic and immunological biomarker in several human cancers	Soltan MA, Eldeen MA, Eid RA, Alyamani NM, Alqahtani LS, Albogami S, Jafri I, Park MN, Alsharif G, Fayad E, Mohamed G. A pan-cancer analysis reveals CHD1L as a prognostic and immunological biomarker in several human cancers. Frontiers in molecular biosciences. 2023 Mar 23;10:1017148. doi: 10.3389/fmolb.2023.1017148.	CHD1L as a potential prognostic biomarker and target for antitumor therapy development

DISCUSSION

Head and neck squamous cell carcinomas (HNSCCs) have a yearly incidence of 600,000 cases worldwide, with 40–50% mortality, HNSCC is remarkably heterogeneous.¹

Tobacco chewing, snuff, and the common practice of betel quid consumption dramatically increase oral cancer risks, causing it to account for up to 50% of all cancers in certain Indian subpopulations.² Carcinogens directly cause specific DNA mutations in crucial genes like *p53*, while alcohol acts as a co-carcinogen by breaking down into DNA-damaging acetaldehyde and blocking the detoxifying peptide glutathione.³

Alcohol induces the CYP2E1 enzyme to activate procarcinogens in drinks and smoke, while marijuana's role in oral cancer remains unproven.⁴

Low fruit and vegetable intake contributes to HNSCC development, driving higher and faster-growing incidence rates in socially deprived communities compared to affluent ones.⁵

High-risk HPV types in oral cells increase HNSCC risk, acting synergistically with heavy alcohol consumption and additively with tobacco use, though the virus's overall role in the disease remains a subject of ongoing discussion.⁶

While traditional cytogenetic studies identified the majority of known cancer genes, high-throughput sequencing has uncovered new drivers such as BRAF, EGFR, and PIK3CA.⁷

Specifically, in HNSCC, studies confirmed known alterations in TP53 and CDKN2A while identifying NOTCH1 as a novel, frequently mutated gene.⁸

Given the heterogeneous nature of HNC generally and HNSCC specifically, the targeted therapies and molecular oncological pathways, will result in better outcomes for patients.⁹

The potential of molecular profiling is tremendous, with family-based history, gene expression pathways, and drug resistance and toxicity is considered in treatment plan.¹⁰

Understanding of the mutational and genomic landscape of HNSCC has enabled better use of therapies and, immune checkpoint inhibitors, and will have targeted approaches.¹¹

Currently the optimal treatment includes multidisciplinary approach, medical oncology, radiation oncology, in addition to allied health disciplines.¹²

Targeted treatments have benefitted only a small subgroup of patients due to intrinsic and extrinsic drug resistance with limited drug efficacy.¹³

Identification of new molecular targets and novel pharmacotherapies, as well as better patient selection, calls for new methods of identification and clinical validation of biomarkers.¹⁴

Next-Generation Sequencing (NGS) allows for simultaneous, multi-level evaluation of cancer genomes, enabling faster and more cost-effective assessment of DNA copy numbers, structural rearrangements, and epigenetic changes like methylation.¹⁵

This technology efficiently sequences whole genomes, exomes, and transcriptomes to detect advanced cellular alterations, including loss of heterozygosity, aberrant splicing, and RNA editing, far outpacing traditional Sanger-based methods.¹⁶

Genomic alterations collected by the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA) projects, in addition to the Catalog of Somatic Mutations in Cancer (COSMIC) database provide the most comprehensive source of somatic mutations in cancer.¹⁷

All cells harbour a number of genes with the potential to become dominant transforming genes or oncogenes. The first oncogenes to be recognized were the coopted cellular genes responsible for most retrovirally induced tumors.¹⁸

Oncogenes are categorized into retroviral origins and those from non-viral tumors; while most are viral, families like *ras* reveal structural overlap, whereas other tumor oncogenes remain entirely distinct.¹⁹

Cellular proto-oncogenes are highly conserved across evolution, signifying that they control critical biological functions which promote malignant phenotypes when altered or disrupted.²⁰

The CHD1L protein is a chromatin remodeling enzyme whose structure reveals unique regulatory features distinguishing it from other CHD family members, also they exist under the umbrella of the SNF-2 (sucrose non-fermentation 2) superfamily.²¹

There are two highly conserved signature motifs characteristic of the CHD family: N-terminal tandem chromodomains and a centrally located SNF2-like ATPase domain (SNF2-N).²²

The CHD N-terminal chromodomain binds methylated histones while its ATPase domain uses energy to move histones along DNA, assisted by a C-terminal DNA-binding helicase superfamily domain (HELICc) found in CHD1 and CHD2 subtypes.²³

There are 9 subtypes of the CHD family, which are numbered CHD1–9, and CHD1L is named as such because of its high similarity to CHD1, particularly within the helicase domain.²⁴

Multiple lines of evidence, including site-directed mutagenesis and transcript variant analysis, have revealed key features of CHD1L's regulatory mechanisms and chromatin remodeling function, also involved in autoinhibition and activation.²⁵

In addition to point mutations, CHD1L function may be influenced by transcript diversity. At least six splice variants have been identified, each altering the inclusion of critical functional domains.²⁶

CHD1L plays a critical role in early embryonic development, where it orchestrates chromatin remodeling programs essential for cellular plasticity, pluripotency, and tissue morphogenesis.²⁷

These developmental functions rely on CHD1L's chromatin remodeling, a mechanism later exploited in cancer to drive transcriptional reprogramming and tumor progression.²⁸

Prior to implantation, the zygote requires temporary totipotency to accomplish the extensive development ahead, and complex chromatin organization does not favour this state.²⁹

Thus, chromatin remodelers that increase DNA accessibility are upregulated in the pre-implantation embryo.³⁰

CHD1L expression peaks late in the morula stage of development and knockdown of CHD1L prior to the blastocyst formation will lead to developmental arrest.³¹

The post-translational modification of PARylation via PARP1 regulates cell reprogramming by activating key stemness and pluripotency genes like OCT4, SOX2, KLF4, and c-MYC.³²

PARP1 recruits CHD1L to these pluripotent loci, suggesting its nucleosome remodeling function is key for the activation of these genes and cellular reprogramming towards a state of stemness.³³

CHD1L is expressed in many growing organs, but mainly in the developing brain. It upregulates PAX6, in particular, a transcription factor critical to forebrain development.³⁴

CHD1L has been associated with the expression of genes involved in the development of the ectoderm, the outermost layer that ultimately gives rise to the epidermis and nervous system.³⁵

It contributes to many hallmarks of cancer, including enhanced survival, evasion of programmed cell death, metastatic potential, evasion of the immune response, and MDR.³⁶

The overexpression of CHD1L in a wide range of malignancies, and this overexpression is strongly associated with tumor progression, metastatic disease, and poor clinical outcomes for breast, ovarian, bladder, lung, colorectal, and many other cancer indications.³⁷

CHD1L has a variety of oncogenic functions that promote tumor progression, metastatic potential, cancer cell survival, and resistance to treatment.³⁸

Clinical studies show that *CHD1L* is associated with more aggressive behavior and poor prognosis across multiple cancer types, a correlation heavily studied in gastrointestinal tumors but seen in other malignancies as well.³⁹

Studies of patient tumor samples report CHD1L overexpression in breast, pancreatic, non-small cell lung, and many other cancer indications.⁴⁰

Therefore, studying the CHD1L transcriptional regulation network helps to elucidate the oncogenic molecular mechanisms of CHD1L, and may further provide new therapeutic targets for cancer treatment.⁴¹

Overexpression of the CHD1L gene has also been observed in 40%-50% of cutaneous squamous cell carcinoma patients.⁴²

The overexpression of CHD1L has been associated with more aggressive tumor behavior and poorer prognosis in cutaneous squamous cell carcinoma.⁴³

Research has shown that CHD1L has a variety of roles in the development of HCC, including stimulating cell invasion and migration in breast cancer via the PI3K/AKT/ARK5/mTOR/MMP pathway.⁴⁴

CHD1L may stimulate cell migration and the advancement of the cell cycle via the MDM2/p53 pathway and promotes exosome secretion through PI3K/AKT pathway.⁴⁵

As a key immune inhibitory regulator, PD-L1 is linked to exosome secretion, PI3K/ AKT, and T cell activation during immunological responses via binding to PD-1 on T cells.⁴⁶

The role of CHD1L in tumor progression, cell survival, metastasis, and MDR makes it an attractive molecular target for the next generation of cancer treatments.⁴⁷

Knockdown of CHD1L dramatically reduces the aggression and growth of cancerous cells, while concurrently sensitizing them to chemotherapy.⁴⁸

This indicates the strategy of CHD1L suppression could be valid as either a single agent therapy or combination therapy.⁴⁹

Although there are no CHD1L-related treatments on the market to date, there are several that have been proposed or are currently in development that may well drive forward the field of targeted cancer therapy.⁵⁰

CONCLUSION

Cutaneous squamous cell carcinoma (SCC) is the second most common type of skin cancer, behind basal cell carcinoma. 5–10% of SCC cases have a bad prognosis that includes disease-specific mortality, lymph node metastases, and local recurrence, despite the fact that the majority of patients have a fair prognosis with appropriate therapy. Sun-exposed regions like the face and backs of the hands are common sites for SCC. It is uncommon in teenagers and more common in men and older

people. Lesions may appear as plaques, ulcers, or nodules. UV radiation, persistent inflammation, persistent infection, exposure to carcinogens, and human papillomavirus (HPV) infection are common causes. However, there aren't many reliable markers to predict the biological behavior and clinical outcomes of SCC. Therefore, identifying biomarkers and better understanding the molecular mechanisms underlying SCC are crucial to developing effective treatment plans for the disease. In the hypoxic environment of cutaneous squamous cell carcinoma, CHD1L can stimulate cancer cells to secrete PD-L1, which in turn stimulates the ERK/AKT/mTOR signaling pathway and M2 polarization in tumor-associated macrophages. This inhibits M1 polarization and causes cutaneous squamous cell carcinoma cells to proliferate, migrate, invade, and undergo angiogenesis. In order to augment the results of this investigation and provide novel targets for immunotherapy of cutaneous squamous cell carcinoma.

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