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The Cytidine Deaminase-Dependent and Independent Effects of APOBEC3A in Head and Neck Squamous Cell Carcinoma: A Literature Review

Parth Arora, HBSc Student [1], Florence Deng, BHSc Student [2],
Aditya Misra, HBSc Student [1]*

[1] Faculty of Science, McMaster University, Hamilton, Ontario, Canada L8S 4L8
[2] Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada L8S 4L8

*Corresponding Author: misraa7@mcmaster.ca

Abstract

Introduction: Head and neck squamous cell carcinoma (HNSCC) is a prevalent and aggressive cancer affecting mucosal linings, with increasing incidence in younger populations. Risk factors include tobacco, alcohol, and human papillomavirus (HPV) infection. Current treatments often result in significant side effects and limited success in preventing recurrence and metastasis. This study investigates the role of APOBEC3A, a cytidine deaminase, in HNSCC tumorigenesis, focusing on both deaminase-dependent and independent mechanisms.

Methods: A systematic literature review was conducted, searching PubMed, Web of Science, Embase, and Cochrane Library databases for relevant studies published between 2013 and 2024. Key terms included "APOBEC3A," "cytidine deaminase," "cancer," and "oncogenesis." Articles involving experimental studies with human tumor samples, in vitro and in vivo models, and clinical studies were included. Data were extracted on study design, methods, and findings related to APOBEC3A's role in HNSCC.

Results: APOBEC3A contributes to HNSCC through deaminase-dependent mechanisms, inducing C-to-T and C-to-G mutations, particularly in TP53 and PIK3CA genes, which are associated with tumor progression and resistance to therapies. Additionally, APOBEC3A's interaction with HPV further exacerbates genetic instability, leading to more aggressive tumor behavior. Deaminase-independent roles include modulation of the tumor microenvironment, influencing immune cell interactions and promoting immune evasion through cytokine production and PD-L1 expression.

Discussion: APOBEC3A's dual roles in HNSCC highlight its significance in both promoting oncogenic mutations and modulating immune responses. The enzyme's activity not only contributes to tumorigenesis through direct genetic alterations but also indirectly by creating a favorable environment for tumor growth and survival.

Conclusion: This study underscores the critical role of APOBEC3A in the pathogenesis of HNSCC and the need for targeted therapies addressing both its enzymatic and non-enzymatic functions. Future research should explore therapeutic strategies that inhibit APOBEC3A's activity and counteract its contributions to immune evasion and tumor progression.

Keywords: head and neck squamous cell carcinoma; APOBEC3A; cytidine deaminase; oncogenesis; immune evasion; HPV; tumor microenvironment; genetic instability; PD-L1; cancer therapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a group of aggressive cancers that develop from mucosal linings of the oral cavity, pharynx, and larynx [1]. HNSCC is responsible for around 4.5% of cancer diagnoses and deaths, with an estimated 890,000 new cases around the world and 450,000 deaths annually [2, 3]. Globally, HNSCC is more prevalent in men than women, and in adults over 50 years of age [3]. However, HNSCC rates are on the rise in younger populations, with studies predicting a 30% annual increase by 2030 [3]. These shifting epidemiological trends underscore the urgency of identifying new molecular markers and therapeutic targets, driving the need for a more nuanced understanding of HNSCC pathogenesis in diverse patient populations.

Risk factors for HNSCC include tobacco use, alcohol consumption, and human papillomavirus (HPV) infection. The current standard of care for HNSCC is radiotherapy and surgery for patients in Stage I and Stage II of disease [4]. In Stage I, the tumor is small (2 cm or less in diameter) and has not spread to lymph nodes or other parts of the body. In Stage II, the primary tumor is larger than 2 cm but not more than 4 cm in diameter [4]. Stages III and IV are characterized by metastasis to lymph nodes or other parts of the body and treatment typically involves concurrent chemoradiation therapy, often supplemented with targeted

therapies such as cetuximab [5]. Clinical trials have shown that cetuximab, when used with radiation therapy, significantly reduces the risk of disease progression or death by 30% ($p = 0.006$), thereby improving progression-free survival [5-7]. Treatment decisions, including the choice between surgery and radiation, are tailored to the patient's specific situation in a multidisciplinary setting [5]. Despite these advancements, comprehensive reviews that integrate the latest immunotherapeutic approaches and molecular-targeted strategies for HNSCC remain limited, highlighting a critical need for in-depth analyses of emerging treatment paradigms.

Managing HNSCC is challenging due to its high rates of recurrence and metastasis. While the available treatments can effectively manage the disease to some extent, they often come with significant side effects that can impact overall patient health and quality of life [8]. Moreover, despite treatment, many patients still face a poor prognosis due to the aggressive nature of the disease itself. Thus, enhanced understanding of the molecular aspects of HNSCC is crucial for developing more effective diagnostic tools and therapeutic strategies that may improve outcomes and reduce treatment-related complications. Addressing these issues holistically and comparing innovative strategies across different stages of HNSCC can help researchers and clinicians identify the most promising avenues for personalized medicine.

Genetic and genomic changes play a key role in the development and progression of HNSCC. Mutations in tumor suppressor genes such as TP53, and oncogenes such as PIK3CA and NOTCH1, as well as the disruption of signalling pathways such as the epidermal growth factor receptor pathway, are known to contribute to HNSCC through promoting uncontrolled cell growth, and evasion of apoptosis [1, 9, 10]. These genetic alterations can also increase tumor aggressiveness by enhancing cellular proliferation, invasion, and metastasis. Understanding the source of genetic alterations that drive HNSCC formation and progression is important for finding new therapeutic targets. In particular, synthesizing insights from diverse genetic studies to highlight common mutational signatures can illuminate novel points of therapeutic intervention and refine existing treatment frameworks.

The Apolipoprotein B mRNA Editing Catalytic Polypeptide-like 3 (APOBEC3) family of cytidine deaminases, particularly APOBEC3A, has been identified as a significant contributor to oncogenic mutations such as PKCα/NF-κB dysregulation pertaining to cell cycle disruptions observed in HNSCC [11]. Normally, APOBEC3A, a member of the APOBEC family, primarily functions in the innate immune system by providing antiviral defence [12]. It edits viral DNA and RNA through cytidine deamination, converting cytosine to uracil. This leads to hypermutation in viral genomes, inhibiting viral replication [13]. APOBEC3A also restricts endogenous retroelements, thereby maintaining genomic stability and protecting against mutagenic events. In addition to these deaminase-dependent mechanisms, APOBEC3A also contributes to innate immune defense through deaminase-independent means, such as modulating other cellular pathways that affect immune response. Through these diverse mechanisms, both deaminase-dependent and independent, APOBEC3A safeguards cellular integrity and defends against viral infections. While several reviews have addressed the APOBEC3 family in general, few have provided a focused examination of APOBEC3A's dual roles in HNSCC, emphasizing both canonical (deaminase-dependent) and emerging (deaminase-independent) pathways. By doing so, this work aims to delineate a more complete molecular profile that could guide future therapeutic development. However, despite its role in protecting the genome, APOBEC3A can paradoxically contribute to oncogenesis. When dysregulated, APOBEC3A, through its cytidine deaminase activity, can induce mutations in tumor suppressor genes and pathways, further driving the genetic diversity and evolution of HNSCC, leading to increased tumor progression and therapy resistance. This paper aims to explore the genetic and molecular factors involved in HNSCC progression and metastasis, focusing on the deaminase dependent and independent means by which APOBEC3A contributes to these processes.

Methods

To investigate the role of APOBEC3A in HNSCC, a systematic literature review was conducted. The databases searched included PubMed, Web of Science, Embase, and the Cochrane Library, targeting articles published in the last decade (2013-2024) to ensure the inclusion of recent and relevant studies. Keywords such as "APOBEC3A," "cytidine deaminase," "cancer," and "oncogenesis" were used in various combinations, along with specific terms related to HNSCC. Boolean operators and Medical Subject Headings (MeSH) terms were employed to refine the search. Articles were limited to those published in English and included experimental studies involving human tumor samples, in vitro and in vivo models, and clinical studies.

Titles and abstracts of identified articles were screened for relevance, followed by a full-text review of validated studies to further assess the significance to the research question. Data were extracted from the included studies regarding study design, experimental methods, sample types, and main findings related to APOBEC3A's role in HNSCC. This comprehensive approach aimed to elucidate the multifaceted role of APOBEC3A in HNSCC pathogenesis.

Results

Deaminase-Dependent Tumorigenesis in HNSCC

In HNSCC, a distinct mutational pattern characterized by C-to-T and C-to-G mutations is often observed [14]. This pattern is notably prevalent in specific trinucleotide contexts, such as TCA and TCT, which indicates a targeted

mutational process [13]. Among the APOBEC family, APOBEC3A has been identified as a key contributor to the mutational landscape of HNSCC. Isozaki et al. studied APOBEC3A mutational burden across cancer cell types and the mechanisms influencing tumor evolution during treatment. They identified that a substantial portion of new mutations in their study exhibited an APOBEC signature, specifically C-to-T and C-to-G substitutions at TpC motifs [17].

Their mutation analysis of patient-derived cell lines demonstrated enriched APOBEC signatures within resistant clones. Isozaki et al. also observed a multifold induction of APOBEC3A expression in non-small cell lung cancer (NSCLC) cell lines, with a strong correlation between APOBEC3A RNA transcription levels and RNA editing [17]. NSCLC and HNSCC are both squamous cell carcinomas and share many phenotypic and molecular characteristics, as well as similar responsiveness to other targeted therapies for both cancers [18, 19]. Similar to HNSCC, increased APOBEC3A activity has been implicated in the mutation landscape of NSCLC, as Isozaki et al. found that digital PCR sensitive to APOBEC3A activity significantly increased C-to-U editing in mutant NSCLC cell lines [20].

Synergy Between HPV Infection and APOBEC3A

Recent studies have demonstrated a synergistic effect between HPV infection and APOBEC3A mutational signatures in driving the oncogenesis of HNSCC [20]. The APOBEC3A mutational signature was observed in 98% of HPV+ HNSCC compared to 76% in HPV- HNSCCs [21]. Bioinformatics analysis of tumor exomes from 511 HNSCC patients highlighted a strong correlation between elevated APOBEC3A expression and increased mutational burden, which was significantly associated with the rate of HPV integration into the host genome and worse clinical outcomes in these patients [10, 22, 23]. HPV infects basal epithelial cells and utilizes the host's DNA replication machinery for viral replication, with HPV33 being a common subtype associated with HNSCC [2, 20]. Concurrently, APOBEC3A induces permanent C-to-T transitions, particularly targeting critical tumor suppressor genes such as TP53 [24, 25]. Studies have identified a high frequency of transition mutations at cytidine bases, missense mutations, and allelic loss within TP53, which are characteristic of APOBEC3A's action.

Multiple studies have reported that APOBEC3A-mediated mutations, especially those within TP53 and PIK3CA, are highly prevalent in HPV+ HNSCC. Point mutations in TP53's binding domain, such as R248W and R273H, can impair apoptosis and facilitate unchecked cell division [39].

Deaminase-Independent Mechanisms

In HNSCC, APOBEC3A influences cytokine production, significantly altering the landscape of immune cell interactions within the tumor [41]. It enhances the production of key cytokines such as interleukin-1 beta (IL1B), which not only promotes the polarization of M1 macrophages, but also supports an inflammatory environment conducive to immune cell recruitment and activation. Upregulation of APOBEC3A, which is commonly observed in HNSCC, has been linked to increased expression of immune checkpoint molecules such as PD-L1 through CD8+ T cell inhibition and PKCα/NF-κB regulation [42]. Additionally, a study by Løvestad et al. indicates that in HNSCC-associated HPV variants, such as HPV33+ HNSCC, there is a reduced infiltration of CD8+ cytotoxic T-cells compared to HPV16+ tumors [43]. TGFB1 is notably higher in HPV33+ tumors compared to HPV16+ tumors [45, 46]. Specifically, Chatfield-Reed et al. showed that CD8+ cytotoxic T-cell infiltration was reduced by 2.7% in HPV33+ tumors compared to HPV16+ tumors ($p = 0.007$) [45].

APOBEC3A modulates dendritic cells and T cells, affecting their functional roles within the immune system and thus impacting the efficacy of immunotherapeutic strategies like checkpoint inhibitors and cellular therapies [23]. Importantly, studies have shown that APOBEC3A, along with other factors like Protein Kinase C alpha (PKCα) and Nuclear Factor kappa B (NF-κB), form a regulatory circuit [49].

APOBEC3A has been shown to influence DNA repair processes and cell cycle regulation independent of its catalytic activity. When Landry et al. analyzed the effect of APOBEC3A expression on downstream substrates within the DNA damage signaling cascade, they found phosphorylated replication proteins within the APOBEC3A-expressing cell signaling cascade [51]. They further demonstrated, through staining and TUNEL assays, that APOBEC3A expression in cells was correlated with observed DNA breakages and cleavages that were not the result of apoptosis. Cells induced for APOBEC3A expression were further noted to enter arrests at the G1 and S stages of the cell cycle.

Discussion

Deaminase-Dependent Tumorigenesis in HNSCC

Mutations associated with the APOBEC family of enzymes, particularly APOBEC3A, result from deamination of cytidine residues in single-stranded DNA, converting cytosine to uracil [15]. This enzymatic activity leads to the formation of uracil during DNA replication, causing C-to-T transitions and, through error-prone repair mechanisms, C-to-G transversions. These mutations contribute significantly to the mutational burden observed in cancer genomes, including HNSCC [16]. APOBEC3A's higher catalytic activity and preference for single-stranded DNA regions, transiently exposed during DNA replication and transcription, make it a potent mutator in the context of genomic instability [16].

These mutations increase genetic diversity, contributing to chemotherapeutic drug resistance by altering drug targets

and generating secondary mutations, such as the T790M mutation in APOBEC3A-induced carcinomas. This activity provides a survival advantage, enabling the selection of resistant cell clones, triggering DNA damage response pathways, and contributing to genomic instability. In extreme cases, this DNA damage can push cells into a quiescent state, rendering standard radiation therapies less effective [17]. Increased APOBEC3A activity may be a response to targeted therapies in oncogene-driven cancer cells, suggesting its role in driving therapy resistance. Given the similarities between the mutation landscapes of NSCLC and HNSCC, APOBEC3A-induced mutations likely contribute to genetic heterogeneity and therapy resistance in both cancers.

Understanding the specific mutations induced by APOBEC3A is crucial for designing targeted therapies that can circumvent or counteract these resistance mechanisms. Although these findings highlight APOBEC3A's pivotal role in driving oncogenesis in HPV-related cancers, further in vivo studies are needed to understand the synergistic role of HPV and APOBEC3A in HNSCC proliferation more definitively.

One of the most frequently mutated genes in cancer, TP53, plays a key role in regulating the cell cycle and apoptosis [26]. Mutations in TP53, especially in the presence of APOBEC3A, compromise p53's tumor suppressor functions [26-28]. In epithelial cells, the loss of function of p53, exacerbated by HPV's E6 oncoprotein, contributes to oncogenesis. E6 binds to p53, facilitating its ubiquitination and degradation, while E7 binds to pRb, inhibiting pRb's ability to regulate the cell cycle by releasing E2F transcription factors [31-33]. As a result, DNA replication and cell division proceed unchecked, leading to genetic abnormalities and promoting oncogenesis [20]. The interaction between APOBEC3A's mutagenic activity and HPV's disruption of cell cycle and apoptosis control highlights the importance of precision medicine approaches in HNSCC treatment [20].

In addition, APOBEC3A interacts with BCL-2, an anti-apoptotic protein, stabilizing it and promoting the survival of genetically altered cells. This interaction prevents the apoptotic clearance of potentially malignant cells, contributing to tumor resilience and complexity [20]. Mutations in PICK3CA, such as E545K and H1047R, lead to enhanced kinase activity and oncogenic signalling, contributing to both tumor growth and therapy resistance [40]. The specific interaction between APOBEC3A, HPV-driven mutations, and the disruption of cell cycle and apoptosis control points to a need for therapies targeting molecular abnormalities caused by APOBEC3A and HPV. Approaches that inhibit APOBEC3A directly or correct mutations in TP53 and PICK3CA may improve therapeutic efficacy and patient outcomes.

Deaminase-Independent Mechanisms and Influence on Tumor Microenvironment

Beyond its genomic mutagenesis, APOBEC3A plays a significant role in modulating the tumor microenvironment in HNSCC. It enhances cytokine production, such as interleukin-1 beta (IL1B), promoting the polarization of M1 macrophages and fostering an inflammatory environment that supports immune cell recruitment and activation [41]. While this creates an immunologically active microenvironment, it simultaneously aids tumor immune evasion. Upregulation of APOBEC3A has been linked to increased expression of immune checkpoint molecules like PD-L1 through CD8+ T cell inhibition and PKCα/NF-κB regulation, further contributing to immune escape [42].

The reduced infiltration of CD8+ cytotoxic T-cells, particularly in HPV33+ HNSCC compared to HPV16+ tumors, suggests that APOBEC3A may also play a role in evading immune surveillance [43]. Elevated TGFB1 levels in HPV33+ tumors, compared to HPV16+ tumors, further suppress T-cell function, diminishing the immune response and complicating immunotherapies [45, 46]. The distinct genomic landscape of HPV33+ tumors, including higher aneuploidy and frequent 3p loss, correlates with these immunological disparities, making this subtype particularly challenging to treat [45].

Moreover, APOBEC3A regulates PD-L1, a protein that binds to PD-1 on CD8+ T cells, inhibiting their activity and enabling tumor immune evasion. Increased APOBEC3A expression leads to higher PD-L1 levels, thereby enhancing the tumor's ability to evade immune responses [47]. Additionally, APOBEC3A modulates dendritic cells and T cells, impacting their functional roles within the immune system and influencing the efficacy of immunotherapeutic strategies like checkpoint inhibitors [23].

Recent studies suggest that under normal physiological conditions, PKCα/NF-κB-mediated regulation plays a crucial role in maintaining immune homeostasis and response to pathogens. However, dysregulation of this regulatory circuit can alter the immunogenicity of HNSCC, potentially aiding tumor growth and immune evasion [50]. Another mechanism by which APOBEC3A affects the tumor microenvironment involves cell cycle regulation through deaminase-independent mechanisms. APOBEC3A's influence on DNA repair and its role in cell cycle arrest at the G1 and S stages indicate its broader impact on genome destabilization [51]. APOBEC3A's role in activating damage kinases and contributing to DNA damage complicates its potential as a therapeutic target, as inhibiting its mutagenic activity could have unintended consequences on cellular homeostasis.

Conclusion

In this paper, we have outlined the significant roles of APOBEC3A in the development and progression of HNSCC. Our systematic review of the literature and analysis of data reveal how APOBEC3A's cytidine deaminase activity contributes to the oncogenic mutations observed in HNSCC and drives genetic diversity thus complicating therapeutic intervention. By detailing its role in inducing key mutations within tumor suppressor genes and oncogenic pathways, we highlight the critical need for

strategies that address dysregulation of APOBEC3A as a preventative measure against HNSCC formation and progression. Moreover, the interplay between APOBEC3A and HPV infection, particularly in modifying the tumor microenvironment and enhancing resistance to conventional treatments such as chemoradiation, underscores the enzyme's impact on clinical outcomes.

Further, our research extends beyond the enzymatic functions of APOBEC3A to explore its deaminase-independent roles, which influence cellular behavior and tumor dynamics through mechanisms like tumor suppressor gene pathways, CD8+ T cell activation, and DNA repair processes. These findings suggest that APOBEC3A contributes to tumor progression not only through direct mutational mechanisms but also by altering head and neck squamous cell homeostasis and division regulatory networks and their immune responses. Our analysis not only deepens understanding of APOBEC3A's roles in HNSCC, but also paves the way for targeted research into novel therapeutic approaches that specifically modulate APOBEC3A's enzymatic and non-enzymatic pathways. Building on these insights, further in vivo experiments are warranted to clarify the synergistic roles of HPV and APOBEC3A in HNSCC proliferation and therapy resistance. Future research should focus on developing targeted interventions that mitigate APOBEC3A-induced mutagenesis, refining immunotherapeutic strategies to address immune evasion mechanisms, and exploring how deaminase-independent pathways can be harnessed to improve patient outcomes. Thus, we highlight the importance of considering both the deaminase dependent and independent means by which APOBEC3A contributes to HNSCC tumorigenesis and progression so that more effective therapies can be developed.

List of Abbreviations

APOBEC3: apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3
BCL-2: B-cell lymphoma 2
C-to-G: cytosine to guanine
C-to-T: cytosine to thymine
DNA: deoxyribonucleic acid
E2F: E2F transcription factor
HNSCC: head and neck squamous cell carcinoma
HPV: human papillomavirus
IL1B: interleukin 1 beta
MeSH: medical subject headings
NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells
NSCLC: non-small cell lung cancer
p53: tumor protein P53
PCR: polymerase chain reaction
PD-1: programmed death-1
PD-L1: programmed death-ligand 1
PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PKCα: protein kinase C alpha
pRb: retinoblastoma protein
T790M: threonine 790 to methionine mutation
TCA: thymine-cytosine-adenine
TCT: thymine-cytosine-thymine
TGFB1: transforming growth factor beta 1
TP53: tumor protein P53
TpC Motifs: thymidine preceded by a cytosine motifs
TUNEL assays: terminal deoxynucleotidyl transferase dUTP nick end labeling assays

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This study did not require ethics approval.

Authors' Contributions

PA: Made substantial contributions to the design of the study, the collection of data, as well as the analysis and interpretation of data, drafted and revised the manuscript extensively, gave final approval of the version to be published.
FD: Made substantial contributions to the design of the study, the collection of data, as well as the analysis and interpretation of data, drafted and revised the manuscript extensively, gave final approval of the version to be published.
AM: Made substantial contributions to the design of the study, the collection of data, as well as the analysis and interpretation of data, drafted and revised the manuscript extensively, gave final approval of the version to be published.

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