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Review

Exploring the Link between DNA Hypermethylation and HPV in Salivary Gland Tumors

Tükürük Bezi Tümörlerinde DNA Hipermetilasyonu ve HPV Arasındaki Bağlantının Araştırılması

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ABSTRACT

Salivary gland tumors (SGTs) pose considerable diagnostic and treatment challenges due to their heterogeneous nature, diverse histogenesis, and unpredictable clinical outcomes. Benign tumors exhibit a known recurrence rate, whereas malignant tumors are associated with a poor prognosis and a low recovery rate. Nonetheless, despite the growing body of research, there is insufficient evidence to establish a link between SGTs, human papilloma virus (HPV) infection, and the hypermethylation of tumor suppressor genes. The aim of this study is to elucidate the relationship between DNA hypermethylation and HPV in SGTs, elucidate the role of DNA hypermethylation in HPV-associated SGTs, thereby offering insights into novel diagnostic, and prognostic markers. As epigenetic alterations significantly contribute to the development of carcinogenesis, addressing these epigenetic alterations may help in early treatment plans and early detection of SGTs.

Keywords: DNA hypermethylation, epigenetics, salivary gland tumors, human papilloma virus, tumor suppressor genes

ÖZ

Tükürük bezi tümörleri (SGT'ler), heterojen yapıları, çeşitli histogenezleri ve öngörülemez klinik sonuçları nedeniyle tanı ve tedavi açısından önemli zorluklar oluşturmaktadır. Benign tümörlerin belirli bir oranda nüksettiği bilinmekteyken, malign tümörler kötü prognoz ve düşük iyileşme oranıyla ilişkilidir. Bununla birlikte, artan araştırmalara rağmen, SGT'ler, insan papilloma virüsü (HPV) enfeksiyonu ve tümör baskılayıcı genlerin (TSG'ler) hipermetilasyonu arasındaki bağlantıyı kanıtlayacak yeterli kanıt bulunmamaktadır. Bu çalışmanın amacı, SGT'lerde DNA hipermetilasyonu ve HPV arasındaki ilişkiyi aydınlatmak, HPV ile ilişkili SGT'lerde DNA hipermetilasyonunun rolünü açıklamak ve böylece yeni tanı ve prognostik belirteçler hakkında bilgi sağlamaktır. Epigenetik değişiklikler karsinogenez gelişimine önemli ölçüde katkıda bulunduğundan, bu epigenetik değişikliklerin ele alınması, SGT'lerin erken tedavi planları ve erken teşhisinde yardımcı olabilir.

Anahtar kelimeler: DNA hipermetilasyonu, epigenetik, tükürük bezi tümörleri, insan papilloma virüsü, tümör baskılayıcı genler

INTRODUCTION

Salivary gland tumors (SGTs) are rare and heterogeneous in nature, have diverse histogenesis, and show unpredictable clinical outcomes. World Health Organization (WHO) Global Cancer Observatory reported 53,083 new cases diagnosed worldwide in 2020, with an incidence rate of 0.56 and a death rate of 0.23 per 100,000 individual-years[1]. According to GLOBOCAN 2022, SGTs are rated 28th in incidence, comprising 0.56% of all cancer types. The mortality rate ranks 27th, with 23,942 fatalities, constituting 0.2% of all cancer locations[2]. Due to their morphological heterogeneity, encompassing over twenty recognized histologic subtypes, the diagnosis of such conditions is challenging and necessitates a combination of extensive molecular profiles and histological techniques. While a significant number may originate from minor salivary glands, the predominant region of SGTs is the major salivary glands (including parotid, submandibular, and sublingual glands). Most of these tumors are malignant and might be identified throughout the mucosal lining of the oral cavity[3].

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Importance of Epigenetic Modifications in SGTs

Epigenetics refers to heritable changes in gene expression that occur independently of alterations to the DNA sequence[4]. Genetic and epigenetic mechanisms are primarily responsible for the modifications in gene expression. Epigenetic modifications occur at the transcriptional level, whereas genetic alterations typically involve changes in the quantity or structure of specific genes. Methylation of CpG islands in the promoter region is a common epigenetic mechanism for regulating gene expression. CpG methylation has been shown in SGTs, oral squamous cell carcinoma, and esophageal squamous cell carcinoma as it influences the development of the tumor. This CpG methylation leads to inhibition of tumor suppressor genes (TSGs) such as p16, *MGMT*, *DAPK*, and *RASSF1A* which may cause DNA hypermethylation[5]. DNA methylation modifications influence the structure of DNA without modifying the genetic code, DNA hypermethylation is much resilient than other epigenetic alterations, rendering it a dependable biomarker for diagnostic applications, this variance is essential due to its significant implications[6]. Besides participating in multiple physiological processes, such as cell differentiation and embryogenesis, epigenetic modifications can also play a role in pathological conditions, including cancers (particularly SGTs) and disrupted cellular states[7]. Epigenetic alterations significantly influence the pathophysiology of SGTs and can potentially be utilized for targeted therapies. It could also serve in prognostic and diagnostic applications[8]. It is evident that, given the vast epigenetic reprogramming occurring during gametogenesis and embryogenesis sensitivity of these reactions, perturbations in this reprogramming could have substantial clinical consequences. Epigenetic modifications transpire throughout folliculogenesis and embryogenesis; thus, any disruption in the natural process throughout these critical phases may result in epigenetic alterations[9]. Several other mechanisms also contribute to the etiology of SGTs, including chromosomal translocations[10], deletions[11], point mutations[12], gene amplifying mutations[13], and epigenetic modifications[14].

Epidemiology and Categorization of SGT

SGTs comprise a varied collection of benign and malignant neoplasms distinguished by diverse, occasionally overlapping, unpredictable, and histological characteristics. Numerous molecular alterations are also observed[15]. In the year 2020, the male-to-female ratio was approximately 1.3:1 for these tumors. They exhibit a stable incidence rate according to epidemiological data, but are also more frequently identified in older individuals. A comprehensive method is typically employed in medical care, encompassing systemic therapies, radiation, and surgery tailored to the patient and the tumor's characteristics[16]. The classification of SGTs entails differentiating among major and minor salivary glands and determining whether tumors are benign or malignant. Clinicians often refer to "80/20 rule" for SGTs, which includes 80% of benign[17], with 70% originating from the parotid gland, around 10% in the submandibular gland, and less than 1% in the sublingual gland. Pleomorphic adenomas (PA) represent the predominant subtype of SGTs, accounting for 65% of cases and approximately 55% of large gland neoplasms and 50% of small gland neoplasms[18]. Warthin's tumors are the second most prevalent benign salivary tumors, mostly impacting the parotid gland, where they constitute 25-32% of its occurrences. They predominantly occur in Caucasian males with a smoking history, with ten to fifteen percent exhibiting bilateral presentation[19].

The histopathological variation among SGTs, which includes many subtypes categorized by WHO[17], poses obstacles in identifying and treating these tumors[20]. SGTs are typically classified as high-grade or low-grade depending on their conduct, which may vary from non-aggressive to aggressive. Approximately 70% of malignant SGTs arise in the parotid gland, 8% in the submandibular gland, and 22% in minor salivary glands[21]. Mucoepidermoid carcinoma (MEC) is among the most common malignant tumors, accounting up to 30% of parotid malignancies[22]. Adenoid cystic carcinoma (AdCC) is the next most prevalent malignant neoplasm of the salivary glands, generally manifesting during the fourth and fifth decades of life[23]. Acinic cell carcinoma, a low-grade neoplasm, constitutes 10-15% of parotid tumors and typically exhibits a protracted progression; nonetheless, it may demonstrate increased aggressiveness in the parotid gland compared to minor salivary glands. Salivary ductal carcinoma is an uncommon yet extremely aggressive neoplasm, primarily impacting older males, and linked to a dismal prognosis[24], evidenced by a 5-year mortality rate of 43%[25]. Carcinoma ex pleomorphic adenoma is an uncommon malignancy originating from persistent or repeated PA, with its prevalence increasing from 1.5% after five years to 10% after fifteen years[5].

The Implications of Hypermethylation in SGTs and Tumor Suppressor Gene Silencing

Hypermethylation leads to the silencing of a substantial number of TSGs which are essential in controlling the hallmarks of carcinogenesis in human cancers[26]. DNA methylation has been associated with several SGTs, both malignant and benign[27]. The epigenetic control of TSGs is being extensively investigated as a possible contributor

to the neoplastic development of salivary glands. The knockdown of TSGs is crucial in neoplasm progression because of their functions in controlling the cell cycle, apoptotic induction, DNA repair, and metastasis inhibition[28]. Despite extensive research on TSGs, their precise actions are still not fully elucidated[29]. However, aberrant methylation of promoter genes is recognized as one of the prevalent causes of TSGs silencing, acting as a catalyst during the initial phases of carcinogenesis[30]. This atypical methylation may facilitate the rendering of particular methylation patterns and is useful not just as a diagnosis and prognosis indicator but also as prospective treatment target[31]. Recent molecular investigations have enhanced comprehension of the significance of DNA methylation in the pathogenesis of SGTs as a mechanism for gene silencing[14]. The methylation status could indicate a new contributing element; however, additional research is required to elucidate its relationship with TSGs[32].

Research Connecting DNA Hypermethylation in SGTs Prognosis

DNA hypermethylation may function as a significant biomarker for monitoring tumor growth, forecasting malignancy, and offering prognostic information[33]. This molecular alteration results in the transcriptional suppression of promoter regions in TSGs[34]. Studies have repeatedly demonstrated that hypermethylation in TSGs such as *MGMT* and *DAPK* occurs in a substantial proportion of SGTs, suggesting its possible involvement in tumorigenesis and prognosis. It exhibits diverse expression patterns that occasionally are associated with tumor aggressiveness and clinical outcomes[35]. Hypermethylation of *MGMT* and *DAPK* frequencies range from twenty percent to forty percent in particular types of tumors such as AdCC and MEC. This methylation could be associated with higher-grade tumor behavior and a worse prognosis[36]. Healthy salivary samples often lack a methylation index; however, benign tumors such as PA and Warthin tumors exhibit methylation in genes like *RASSF1*, *MGMT*, and *DAPK*[37]. Table 1 summarizes malignant and benign SGTs and their prevalence highlighting associated genetic alterations and methylation patterns, reflecting emerging insights into their molecular etiologies.

Overview of Human Papilloma Virus (HPV) Infection in Tumorigenesis and Its Epigenetic Role in SGT: Contemporary Evidence

Human papilloma virus (HPV) is a small, circular, double-stranded DNA virus that primarily targets cutaneous and mucosal epithelial tissues. Although the complete mechanism of HPV infection remains incompletely understood, the widely accepted model suggests that the virus gains entry through micro-abrasions in the epithelial basement membrane. Following endocytosis, the viral genome is transported to the nucleus, where replication and transcription are

Table 1. Highly prevalent genetic alterations in benign and malignant salivary gland tumor.

No	Tumor type	Genetic alterations/ oncogenes	Methylation pattern	Prevalence	Key role in tumorigenesis	Ref
1	MEC	*MECT1-MAML2, EGFR, HER2*	Hypermethylation and genetic translocations	40-90%	Methylation status linked to tumor progression	(38)
2	AdCC	*EN1, FOXE1, TBX4, PITX1*	Hypermethylation of TSGs	~80%	Methylation status linked to tumorigenesis	(39)
3	SC	*ETV6-NTRK3* fusion	Showed unmethylated results	>90%	No molecular alteration	(40)
4	AciCC	*NR4A3* fusion, *RASSF1*	Hypermethylation	86%	Methylation status linked to tumorigenesis	(37)
5	MSA	*MEF2C-SS18* fusion	NA	>90%	NA	(40)
6	MAC	*AKT1 E17K* mutations	NA	100%	Mutant	(40)
7	Ca ex-Pa	*PLAG1* fusions	NA	73%	Amplification	(40)
8	PA	*PLAG1* fusions, *MGMT, DAPK*	Hypermethylation pattern	>50%	Methylation status partially linked to tumorigenesis	(37)
9	BCA	*CTNNB1*	NA	37-80%	Mutant	(40)
10	SP	*BRAF V600E*	NA	50%-100%	Mutant	(40)

MEC: Mucoepidermoid carcinoma, AdCC: Adeniod cyctic carcinoma, SC: Secretory carcinoma, AciCC: Acinic cell carcinoma, MSA: Microsecretory adenocarcinoma, MAC: Mucinous adenocarcinoma, Ca ex-Pa: Carcinoma ex pleomorphic adenoma, PA: Pleomorphic adenoma, BCA: Basal cell adenoma, SP: Sialadenoma papilliferum, NA: Not applicable

initiated using host cellular machinery. The HPV genome consists of eight open reading frames: six early genes (*E1, E2, E4, E5, E6*, and *E7*) and two late genes (*L1* and *L2*). The early genes are chiefly involved in viral replication, transcription, and modulation of host cellular pathways, while the late genes encode structural proteins essential for capsid formation. Among the early genes, *E6* and *E7* have been extensively studied for their oncogenic potential, particularly their ability to disrupt cell cycle regulation and inhibit tumor suppressor proteins such as p53 and Rb. The late genes, *L1* and *L2*, encapsulate the replicated viral genome into icosahedral virions, which are eventually released through the natural process of epithelial desquamation[41]. HPV infections are often asymptomatic and self-resolving; they can manifest as anogenital warts, respiratory papillomatosis, and precancerous or cancerous lesions in the cervical, penile, vulvar, vaginal, anal, and oropharyngeal regions[42]. In 2019, HPV accounted for around 620.000 new cases of cancer in females and 70.000 in males globally. Those with genital HPV infections exhibit a heightened risk of oral or anal HPV infections[43]. In females with cervical cancer, the virus has potential to be transmitted to their partner's oral cavity during sexual intercourse and eventually to one's own oral cavity[44].

The underlying causes of SGTs remain largely undefined, though various risk factors such as radiation, silica dust rubber chemicals, and viruses including Epstein-Barr virus and HPV are believed to contribute to their development and progression. Most tumors, however, do not have a discernible etiology[45]. Increasing evidence suggests that epigenetic alterations, categorized into five core mechanisms -DNA methylation, histone modification, RNA-based methylation, chromatin remodelling, and regulation by non-coding RNAs- play a significant role in the pathogenesis of these tumors. Notably, similar epigenetic alterations have been consistently observed in HPV-associated cancers, supporting the notion that epigenetic reprogramming is a key feature of HPV-driven tumorigenesis[46]. Recent studies have begun to explore the potential association between HPV infection and the development of SGTs. One case-control study conducted within a Taiwanese cohort investigated this relationship by comparing 416 patients with SGTs to 2,080 matched controls. The findings revealed a higher prevalence of prior HPV infection among cancer cases (10.8%) than in controls (6.2%). After adjusting for sociodemographic and health-related variables, individuals with a history of HPV infection demonstrated an 88% increased likelihood of developing SGTs (odds ratio: 1.885)[47]. These results suggest a possible correlation between HPV infection and increased risk of SGTs. If substantiated, this relationship may carry significant diagnostic and therapeutic implications, with potential relevance to patient prognosis and survival outcomes. However, the causal role of HPV, particularly in driving hypermethylation patterns observed in SGTs, remains unclear. This uncertainty largely stems from the rarity and heterogeneity of these tumors, which continue to challenge large-scale molecular investigations[48].

Possibility of Integrated SGTs Biomarker Strategies

Various diagnostic methodologies are being investigated to enhance the diagnosis and treatment planning for SGTs. The examination of morphology parameters, which include inflammatory biomarkers, such as the systemic immune-inflammation index, the systemic inflammation response index, the platelet-to-lymphocyte ratio, and the neutrophil-to-lymphocyte ratio, and radiomic features obtained from imaging techniques such as nuclear magnetic resonance image sequences and histopathology slides, is conducted as part of prospective diagnostic targets[49]. Furthermore, Artificial intelligence (AI)-enhanced salivary biomarker models are being studied for the detection of oral cancer[50]. Nonetheless, the use of AI in the analysis of SGTs remains in development, primarily due to the limited number of cases available at certain diagnostic centers[51].

CONCLUSION

We conclude that studies establishing correlations, conducting comprehensive clinical trials, and examining the predictive and therapeutic relevance of hypermethylation and SGTs are unclear and vary across study populations. This could be due to multiple reasons, such as geographical locations, environmental factors, and delayed diagnosis, where two-thirds of cases are identified at stage 3 or 4 and the lack of molecular indicators to forecast tumor behavior and facilitate patient stratification for customized treatment[52]. Timely identification and ongoing monitoring substantially influence survival rates and clinical outcomes. Whereas the correlation between methylation and HPV status is promising, it requires more research via more extensive, longitudinal investigations and advanced studies. Advancements in diagnostic imaging, particularly MRI and targeted radiomic signatures, are facilitating the differentiation between benign and malignant SGTs[16]. Epigenetic modifications may contribute to the progression of SGTs. The detection of prognostic markers such as *RASSF1*, *MGMT*, and *DAPK* may aid in early cancer treatment strategies, potentially resulting in better treatment outcomes for patients. Further studies

are warranted to better understand their role in tumor development and progression in SGTs.

Footnotes

Author Contributions

Surgical and Medical Practices: A.A.M.Z., R.M., N.M.L., Concept: S.S., A.A.M.Z., N.M.L., Design: A.M., N.M.L., Data Collection and/or Processing: A.M., Analysis or Interpretation: A.M., Literature Search: A.M., Writing: A.M.

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