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REVIEW

Global Dentistry

An overview and molecular taste of oral squamous cell carcinoma

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Abstract

Oral squamous cell carcinoma is the most common oral cancer worldwide. This disease occurs when oral epithelial cells break cell cycle control and form malignant lesions that proliferate indefinitely. Despite continuing research, oral cancers remain a global problem with insignificant improvement in treatment and survival over the last few years. Studying the molecular mechanisms and behaviors may provide insight for potential ways to enhance treatment options, strategies, and prevention. In this review, we will elaborate on current understandings of the molecular mechanisms behind disease development and some of the molecular strategies to target oral squamous cell carcinoma that are currently undergoing investigation.

Keywords: *oral squamous cell carcinoma; oncogenes; tumor suppressor; HPV; alcohol; smoking; tobacco; chemotherapy; radiation; nanoparticles; immunotherapy; checkpoint inhibitors; CAR-T cell therapies*

Introduction

Oral cancers pose a challenge for timely diagnosis, treatment, and prognosis in dentistry and global public health. Despite ongoing research and therapeutic progress, it remains a top-ranking global problem that has lacked significant improvement during the last years [1]. The dismal 5-year survival rate continues to stay below 50% in several countries [2]. Of all head and neck cancer cases, oral cancer accounts for nearly fifty percent of them. Ninety percent of oral cancers are identified as oral squamous cell carcinomas (OSCCs), which are defined as oral cavity, oropharynx, or lip malignant neoplasms that histologically originate from squamous cells [3,4]. High treatment failure of oral cancers is often attributed to delayed clinical detection and the spread of genetically altered cells, leading to secondary tumors [5]. It is estimated that half of oral cancers develop from premalignant lesions [6]. Cancer is known to develop from genetic changes that disable growth control and promote continuous cell proliferation. In addition to genetic alterations, failure of apoptosis and signaling pathways may also contribute to cell survival. Traditionally, oral cancers are treated with a combination of chemotherapy, radiation therapy, and surgery [7]. However, increased understanding of cellular and molecular changes and targets will potentially expand treatment options, disease detection, and diagnosis [8]. Another key element of approaching oral cancers is prevention. Oral hygiene, smoking, alcohol, and use of tobacco are considered major risk factors for OSCC development. These toxic substances introduce deleterious exposure to mutagens that increase DNA damage, that can potentially disrupt cell cycle control [9]. In this review, we will elaborate on the molecular mechanisms and risks that lead to disease development, along with the current treatments and challenges associated with OSCC.

From molecular mechanisms to disease development

Normal healthy squamous cells may undergo carcinogenesis to form premalignant cells, which transform into malignant cells that are characterized by autonomous cell proliferation. Eventually, malignant cells may invade basement membranes and use blood and lymphatics as a highway to infiltrate other tissues [10]. For example, Sharma et al. observed that patients' oral cavity cancer often metastasizes and invades neck nodes [11]. Carcinogenesis or oncogenesis is influenced by both genetic and epigenetic factors. Spontaneous DNA mutations and chromosomal alterations potentially alter protein shape and function. However, prior to cancer development, several DNA mutations are usually accumulated before a cell's normal behaviors, and cell cycle controls are overridden to fuel the creation of malignant cells [12].

Proto-oncogenes are normally, expressed genes that can be converted into constitutively activated oncogenes. Typically, a gain-of-function mutation facilitates the conversion, leading to continuous expression that may induce strain on cell cycle control. The gain-of-function is most often derived from point mutations, chromosomal translocation, or gene amplification [13]. Several examples of oncogenes are RAS pathway genes (*PRAD-1, bcl, int-2*, and *c-myc*) and epidermal growth factor receptor (EGFR) [14-17]. Saranath et al. found that OSCC patients had 3- to 8-fold increase of EGFR levels, implying involvement in oncogenesis [18]. Tumor suppressor genes (TSGs), like oncogenes may also be responsible for OSCC. TSGs are negative regulators of the cell cycle. Examples include p53, RB1, and cyclin-dependent kinase inhibitors [13]. TSGs are usually inactivated when both copies are disrupted by deletions, rearrangements, or point mutations [19]. Loss of function mutations in TSGs drive cell cycle dysregulation and are found in numerous cancers, including oral cancers [20].

Human papillomavirus (HPV) infection is widely prevalent and associated with increased oropharyngeal cancer risk and is the most common sexually transmitted disease that infects roughly 14 million new individuals yearly [21]. Human papillomavirus associated with head and neck squamous cell carcinoma often originates in the palantine and lingual tonsils of the oropharynx [22]. A commonly-found strain of HPV found in oropharynx tumors is HPV-16. The viral genome is known to contain early genes (*E1-E7*). The protein E6 increases p53 ubiquitylation and proteasomal degradation. Also, HPV-positive tumors often present loss of TRAF3 function, which normally facilitates anti-viral immunity. However, TRAF3 loss may facilitate immune evasion of HPV-positive disease [23].

In addition to alterations in oncogenes, tumor suppressors, and viral infections, signaling pathways may experience modifications that further drive carcinogenesis. Three pathways associated with oral squamous cell carcinoma development are nuclear factor kappa B (NF-κB), PI3K-AKT, and Wnt pathways [24] (Figure 1). Hypoxia elicits NF-κB signaling, which upregulates vascular endothelial growth factor-c (VEGF-C) expression, which is often observed in OSCC. VEGF-C binds with receptor VEGFR-3 to promote angiogenesis [25]. Another signaling pathway to consider is PI3K. The PI3K heterodimer facilitates phosphorylation of the D3 hydroxyl group in the inositol ring of phosphatidyl inositols to convert membrane-bound phosphatidylinositol-(4,5)-bisphosphate (PIP2) to phosphatidylinositol-(3,4,5)-trisphosphate (PIP3) [26]. PIP3 is a secondary messenger that is inactivated when dephosphorylated by PTEN. PTEN recruits serine/threonine kinase AKT, which promotes cell survival via apoptosis inhibition [26]. The Wnt signaling pathway is involved in a variety of biological functions. Wnt pathway activation occurs after Wnt ligands bind to membrane receptor Frizzled in an autocrine- or paracrine-like manner. After Wnt ligands bind, β-catenin is translocated to the nucleus, resulting in increased gene expression of *survivin*, *c-myc*, and *cyclin D1* to favor cell differentiation, migration, and proliferation [27]. Ongoing research in these signaling pathways may present potential new targets in oral squamous cell carcinoma treatment.

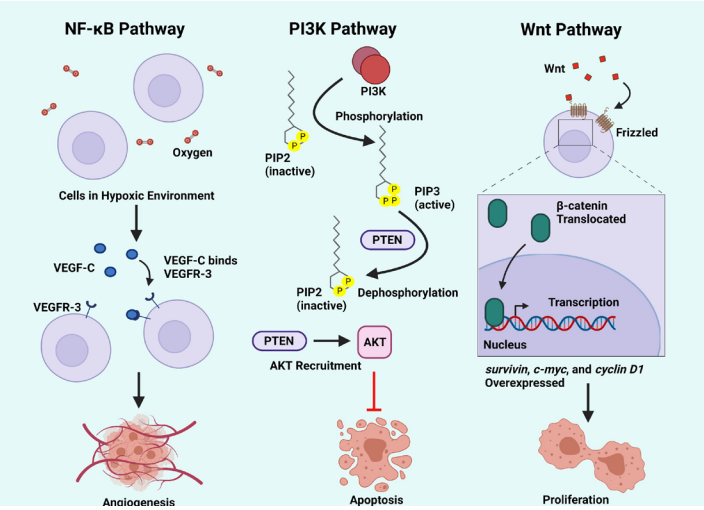

Figure 1. Important signaling pathways that contribute to OSCC development: NF-κB signaling is initiated by hypoxic conditions, leading to increased VEGF-C, which binds surface receptor VEGFR-3, leading to increased angiogenesis. PI3K signaling involves PIP2 transformation to PIP3 by PI3K. PTEN deactivates PIP3 via dephosphorylation converting it back into PIP2. PTEN promotes AKT recruitment, which inhibits apoptosis. Wnt signaling is initiated by Wnt binding to Frizzled, leading to β-catenin translocation to the nucleus, where it induces increased transcription of genes involved in cell proliferation, such as *survivin*, *c-myc*, and *cyclin D1*.

Lifestyle impacts on disease

Lifestyle practices that help assess prognosis of OSCC patients include smoking, drinking, and tobacco chewing. These are important factors to consider in OSCC development because they demonstrate how exposure to harmful substances via lifestyle choices can impact health and propel carcinogenesis forward. Hoes et al. indicated that 26.4% of all the lip and oral cavity cancers are associated with heavy alcohol consumption [28]. Several studies have concluded that acetaldehyde, an established carcinogen, can be metabolized by commensal bacteria found in the oral cavity and within the alcoholic beverage itself [29,30]. Results indicated that higher levels of acetaldehyde were linked to increased formation of adducts and crosslinks in cellular DNA, directly driving mutagenesis [28]. Also, Brennan et al. identified a pattern of p53 mutations in neoplasms from patients with OSCC. The study indicated that among a patient population with a p53 mutation, 58% smoked cigarettes and drank alcohol, while 33% smoked without drinking alcohol [31]. Smoking may impact oral carcinogenesis in several ways. Rodriguez M. et al. found a significant correlation between loss of Methylguanine-DNA-methyltransferase (MGMT) expression and smoking [32]. Other studies suggest that cytochrome P450 enzyme activities can be altered by smoking [33,34]. Tobacco chewing is another behavior that is linked to oral cancer risk. Tobacco can result in oxidative stress, epigenetic alterations in oral epithelial cells, and inhibited immune function [35,36]. One study compared the impact of smoking, alcohol, and other chewing behaviors and revealed that tobacco chewing had the greatest correlation with oral cancer risk and that duration and frequency of alcohol consumption and chewing behaviors may have dose-response relationships with risk [37]. Current and previous research on these lifestyle behaviors and oral cancer is paramount to understanding OSCC risk and possible ways for prevention.

Clinical signs, diagnosis, & prevention

Preventative measures and early diagnosis of any cancer is key to care and treatment. Research shows that oral hygiene is considerably worse in oral cancer patients, resulting in an excess of pathogenic bacteria [38-40]. Daily brushing of teeth and use of floss accompanied by regular dental examinations decreases tumor progression [41]. Most OSCCs will be accompanied by clinical signs that can be identified during standard oral examinations [42,43]. These symptoms include ulceration, tissue damage, discoloration, enlargement of affected site, pain, and loss of function [43]. The five year relative survival rate for those diagnosed with oral cancer is influenced by the tumor stage at time of diagnosis, as well as the time interval between symptom onset and diagnosis [42,43]. Due to this correlation, it is important that both the patient and clinician are alert to potentially malignant lesions, especially when accompanied by other clinical signs [43,44]. In addition to monitoring clinical signs, options for OSCC screening include identifying relevant biomarkers and salivary microRNAs [45,46]. Early diagnosis of OSCC through biomarker detection has the potential to increase survival rate to 80%, as opposed to a survival rate of 20-30% when diagnosed during later stages [46].

Current treatment limitations & solutions

Generally, multiple approaches are used to attack cancer in the clinic. The first treatment option for many OSCC patients will include a chemotherapeutic agent. Chemotherapeutics available for OSCC patients include cisplatin, 5-fluorouracil, and paclitaxel [47]. Unfortunately, many OSCCs will become resistant to anticancer drugs, which demonstrates the importance of treating cancer with multiple strategies [48,49]. Surgery is a common option that is usually followed up by post-operative radiotherapy to prevent reoccurrence of the cancer [50]. A recent study conducted during follow-up of OSCC patients, who had previously received a combination of surgery, chemotherapy, and radiation, indicated that 32.7% of patients experienced a recurrence of symptoms between 2 and 96 months after treatment [51]. Since the discovery of immune checkpoint inhibitors and increased interest in CAR-T cell therapies, immunotherapy-based approaches are being further investigated for OSCC treatment. One option in immunotherapy is the targeting of immune checkpoint signals from tumor cells. Anti-PD-1 antibodies

are examples of this strategy for treating OSCC. The PD-1 molecule on the surface of some immune cells leads to an attenuated immune response when in contact with the PD-1 ligand expressed on cancer cells. PD-1 antibodies target checkpoint signals from tumor cells and have been shown to increase survival rates better than some standard chemotherapies [52]. Research is ongoing for other possible targets in immune checkpoint signaling. Another solution for both drug resistance and non-specific cell apoptosis is using drug delivery platforms with nano mechanisms [47,53]. Nanoparticles are natural or artificial polymeric particles, spherical in shape and ranging in size. These particles are being developed for transcellular transport, especially as drug delivery carriers [54,55]. Nanoparticles can be used in combination with chemotherapies, radiation, or immunotherapy for a more personalized treatment. Possible targeting of OSCC biomarkers are being explored in conjunction with nanomedicine [56,57]. Another treatment strategy under investigation is the targeting of circular RNAs due to their role in the circRNA-miRNA-mRNA signaling axis and its involvement in OSCC development and progression [58]. These targeted treatments will potentially expand treatment options in the clinic. In addition to having a variety of strategies, one study showed the importance of having a high-volume surgeon (or a surgeon that performs several oral surgeries annually) was significantly correlated with overall survival in OSCC patients. The high-volume surgeons were believed to be more competent in surgery and have a greater impact on survival compared to access to different reconstructive and surgical techniques [59]. More variation and improvement in treatment approaches will play a key role in improving survival and preventing cancer reoccurrence in OSCC patients.

Conclusion

Although OSCC remains a global health problem, new research continues to expand understanding of molecular mechanisms involved with oral cancer. Prevention will continue to play a critical part on disease development and research focusing on new treatments will modify current approaches to help provide better strategies to increase OSCC survival. New targets and targeting strategies continue to demonstrate great potential to finally make significant improvements in survival rates in OSCC patients on a global level.

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