Exploring the Molecular Mechanisms of Nicotine in Promoting Oral Squamous Cell Carcinoma Progression

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Abstract

Oral squamous cell carcinoma (OSCC) is a prevalent malignancy with a substantial global burden and poor prognosis, particularly in advanced stages. Tobacco smoking and its principal component, nicotine, have been implicated as significant risk factors for OSCC development and progression. This comprehensive research article delves into the intricate molecular mechanisms through which nicotine contributes to the advancement of OSCC. By examining various cellular pathways, signaling cascades, and epigenetic modifications, we aim to elucidate the multifaceted roles of nicotine in promoting tumor growth, invasion, metastasis, and therapeutic resistance. Emphasis is placed on the interplay between nicotine and key oncogenic pathways, such as the PI3K/Akt/mTOR, MAPK, and NF-κB signaling cascades, as well as its effects on epithelial-to-mesenchymal transition (EMT), angiogenesis, and immune evasion. Additionally, the potential involvement of nicotine in modulating the tumor microenvironment and its implications for cancer stem cell maintenance are explored. Through a comprehensive analysis of the current literature and experimental findings, this article provides valuable insights into the molecular underpinnings of nicotine's protumor genic effects in OSCC, paving the way for the development of novel therapeutic strategies and preventive measures.

Introduction

Oral squamous cell carcinoma (OSCC) poses a significant burden on global public health, representing a considerable proportion of head and neck malignancies across diverse populations. Despite notable progress in diagnostic methodologies and therapeutic modalities, the overall prognosis for patients afflicted with OSCC remains disheartening, especially in cases diagnosed at advanced stages. The dismal 5-year survival rate underscores the pressing imperative for elucidating the intricate molecular pathways driving OSCC progression. A nuanced comprehension of these underlying mechanisms is indispensable for the formulation of targeted therapeutic interventions aimed at mitigating disease progression and improving patient outcomes [1]. The complexity of OSCC pathogenesis necessitates a multifaceted approach integrating molecular, cellular, and clinical perspectives to unravel the intricacies of tumor development, invasion, and metastasis, thus paving the way for the development of novel therapeutic strategies tailored to combat this formidable disease entity [2].

Tobacco smoking remains a significant risk factor for the development and progression of oral squamous cell carcinoma (OSCC), largely due to the exposure of the oral cavity to a multitude of carcinogenic compounds present in tobacco products. Among these

compounds, nicotine stands out as the principal alkaloid and has been extensively studied for its role in the addictive properties of smoking. However, recent research has unveiled a more nuanced understanding of nicotine's involvement in OSCC pathogenesis. Beyond its addictive effects, nicotine appears to exert direct influences on OSCC progression and metastasis through intricate molecular pathways [3]. These pathways involve various cellular processes such as proliferation, angiogenesis, and epithelial-mesenchymal transition (EMT), which collectively contribute to the aggressiveness and invasiveness of OSCC. Thus, while nicotine addiction remains a formidable challenge in smoking cessation efforts, its role as a promoter of OSCC progression underscores the need for comprehensive strategies targeting both addiction and cancer biology to effectively mitigate the burden of OSCC associated with tobacco use [4].

Moreover, the intricate molecular mechanisms through which nicotine promotes OSCC progression present potential therapeutic targets for intervention. By elucidating these mechanisms, researchers aim to identify novel strategies for inhibiting or reversing the deleterious effects of nicotine on OSCC pathogenesis. This may involve targeting specific molecular pathways or cellular processes that are dysregulated by nicotine exposure, thereby attenuating the aggressiveness and metastatic potential of OSCC. Additionally, understanding the interplay between nicotine and other risk factors, such as alcohol consumption and human papillomavirus (HPV) infection, could provide further insights into the complex etiology of OSCC and inform personalized approaches to prevention and treatment [5]. Overall, unraveling the multifaceted roles of nicotine in OSCC pathogenesis not only enhances our understanding of the disease but also holds promise for the development of targeted therapies aimed at improving outcomes for patients with OSCC [6].

Nicotine exerts its effects by binding to nicotinic acetylcholine receptors (nAChRs), which are widely expressed in various cell types, including cancer cells [7]. Activation of these receptors triggers a cascade of intracellular signaling events that can modulate a diverse array of cellular processes, such as proliferation, survival, migration, invasion, and angiogenesis – all of which are hallmarks of cancer progression.

In this comprehensive research article, we will explore the multifaceted roles of nicotine in driving OSCC progression through its interactions with various molecular pathways, cellular processes, and the tumor microenvironment [8]. By elucidating the underlying mechanisms, we aim to provide valuable insights that may pave the way for the development of novel therapeutic strategies and preventive measures targeting nicotine mediated OSCC progression [9].

Nicotine and Oncogenic Signaling Pathways:

The PI3K/Akt/mTOR Pathway: The phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway plays a pivotal role in regulating cellular processes such as proliferation, survival, metabolism, and protein synthesis. Aberrant activation of this pathway is frequently observed in various cancers, including OSCC, and is associated with tumor progression and therapeutic resistance.

Nicotine has been shown to activate the PI3K/Akt/mTOR pathway in OSCC cells through its interactions with nAChRs. Upon binding to these receptors, nicotine induces the phosphorylation and activation of PI3K, leading to the subsequent activation of Akt and its downstream effectors, including mTOR. This cascade of events promotes cell proliferation, survival, and resistance to apoptosis, thereby contributing to OSCC progression [10]. Moreover, nicotine-mediated activation of the PI3K/Akt/mTOR pathway has been implicated in enhancing the invasive and metastatic potential of OSCC cells. Akt signaling can induce the expression of matrix metalloproteinases (MMPs), which are involved in the degradation of the extracellular matrix, facilitating cancer cell invasion and metastasis. Additionally, the PI3K/Akt pathway has been linked to the regulation of epithelial-to-mesenchymal transition (EMT), a process that enables cancer cells to acquire a more invasive and migratory phenotype [11].

The MAPK Signaling Cascade: The mitogen-activated protein kinase (MAPK) signaling cascade is another crucial pathway implicated in OSCC progression and metastasis. This pathway consists of several interconnected kinase cascades, including the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK pathways, which regulate various cellular processes such as proliferation, differentiation, apoptosis, and migration. Nicotine has been shown to activate the MAPK signaling cascade in OSCC cells through its interactions with nAChRs. Upon binding to these receptors, nicotine can induce the phosphorylation and activation of various MAPK pathway components, including ERK, JNK, and p38 MAPK. Activation of these kinases can lead to the modulation of transcription factors, such as AP-1 and NF-κB, which regulate the expression of genes involved in cell proliferation, survival, and invasion. The MAPK pathway has also been implicated in the regulation of EMT and the promotion of cancer cell migration and invasion. For instance, ERK signaling can induce the expression of transcription factors that drive EMT, such as Snail and Slug, while JNK and p38 MAPK have been linked to the regulation of MMPs and the remodeling of the extracellular matrix [12].

The NF-κB Signaling Pathway: The nuclear factor-kappa B (NF-κB) signaling pathway is a crucial regulator of various cellular processes, including inflammation, immunity, proliferation, and survival. Aberrant activation of NF-κB has been implicated in the development and progression of various cancers, including OSCC. Nicotine has been shown to activate the NF-κB signaling pathway in OSCC cells through its interactions with nAChRs. Upon binding to these receptors, nicotine can induce the phosphorylation and degradation of the inhibitory protein IκB, leading to the nuclear translocation of NF-κB and the transcription of its target genes. Activation of the NF-κB pathway by nicotine has been associated with the promotion of OSCC cell proliferation, survival, and resistance to apoptosis. Additionally, NF-κB signaling has been implicated in the regulation of EMT, angiogenesis, and the production of pro-inflammatory cytokines, all of which contribute to OSCC progression and metastasis. Furthermore, the NF-κB pathway has been shown to interact with other oncogenic signaling pathways, such as the PI3K/Akt and MAPK pathways, creating a complex network of signaling cascades that drive OSCC progression [13].

Table 1: Summary of the effects of nicotine on key oncogenic signaling pathways in OSCC.

Pathway	Effects of Nicotine
PI3K/Akt/mTOR	- Activates the pathway through nAChR binding - Promotes cell proliferation, survival, and resistance to apoptosis - Enhances invasive and metastatic potential - Regulates EMT and MMP expression
MAPK (ERK, JNK, p38)	- Activates the MAPK cascades through nAChR binding - Modulates transcription factors (AP-1, NF-κB) - Regulates cell proliferation, survival, and invasion - Induces EMT and MMP expression
NF-κB	- Activates NF-κB through IκB degradation - Promotes cell proliferation, survival, and resistance to apoptosis - Regulates EMT, angiogenesis, and pro-inflammatory cytokine production - Interacts with PI3K/Akt and MAPK pathways

Nicotine and Epithelial-to-Mesenchymal Transition (EMT):

Epithelial-to-mesenchymal transition (EMT) is a cellular process that plays a crucial role in cancer progression, particularly in the acquisition of invasive and metastatic properties. During EMT, epithelial cells undergo a series of molecular and phenotypic changes, losing their cell-cell adhesion and polarity while gaining migratory and invasive capabilities. This transition is orchestrated by a complex interplay of signaling pathways and transcriptional regulators, which are often dysregulated in cancer cells.

Nicotine has been implicated as a potent inducer of EMT in OSCC cells through its interactions with various signaling cascades and transcriptional regulators. One of the key mechanisms by which nicotine promotes EMT involves the activation of the PI3K/Akt and MAPK pathways, as discussed previously [14]. These pathways can modulate the expression and activity of EMT-related transcription factors, such as Snail, Slug, Twist, and Zeb, which play pivotal roles in suppressing the expression of epithelial markers (e.g., E-cadherin) and inducing the expression of mesenchymal markers (e.g., N-cadherin, vimentin). Additionally, nicotine has been shown to induce the production of transforming growth factor-beta (TGF-β), a potent inducer of EMT, in OSCC cells. TGF-β signaling can activate the Smad transcription factors, which, in turn, regulate the expression of EMT-related genes, further promoting the transition to a mesenchymal phenotype.

The EMT process is closely linked to the acquisition of stem cell-like properties and the maintenance of cancer stem cells (CSCs), which are believed to contribute to tumor recurrence, metastasis, and therapeutic resistance. Nicotine has been implicated in the enrichment of CSCs in OSCC through its ability to induce EMT and modulate signaling pathways involved in CSC maintenance, such as the Wnt, Notch, and Hedgehog pathways. Furthermore, EMT is associated with the remodeling of the extracellular

matrix (ECM), a process facilitated by the increased expression and activity of matrix metalloproteinases (MMPs). Nicotine has been shown to upregulate the expression of various MMPs, including MMP-2, MMP-9, and MMP-14, in OSCC cells, contributing to ECM degradation and facilitating cancer cell invasion and metastasis [15].

Table 2: Summary of the effects of nicotine on epithelial-to-mesenchymal transition (EMT) in OSCC.

Mechanism	**Effects of Nicotine**
Transcriptional Regulation	- Induces the expression of EMT-related transcription factors (Snail, Slug, Twist, Zeb) - Suppresses epithelial markers (E-cadherin) - Upregulates mesenchymal markers (N-cadherin, vimentin)
Signaling Pathways	- Activates PI3K/Akt and MAPK pathways, promoting EMT - Induces TGF-β production and Smad signaling
Cancer Stem Cells	- Enriches cancer stem cell population through EMT induction - Modulates stem cell-related pathways (Wnt, Notch, Hedgehog)
ECM Remodeling	- Upregulates matrix metalloproteinases (MMPs) - Facilitates ECM degradation, invasion, and metastasis

Nicotine and Angiogenesis:

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a critical process in tumor growth and metastasis. Cancers require a constant supply of oxygen and nutrients to sustain their rapid proliferation, and the ability to induce angiogenesis is a hallmark of malignant tumors. In OSCC, nicotine has been implicated in promoting angiogenesis through various molecular mechanisms, thereby contributing to tumor progression and metastatic dissemination.

One of the primary mechanisms by which nicotine promotes angiogenesis in OSCC involves the upregulation of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and its receptors (VEGFRs). Nicotine has been shown to induce the expression of VEGF and VEGFR in OSCC cells through the activation of various signaling pathways, including the PI3K/Akt, MAPK, and NF-κB pathways. Furthermore, nicotine can stimulate the production of other pro-angiogenic factors, such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and interleukin-8 (IL-8), which contribute to the recruitment and proliferation of endothelial cells, as well as the stabilization of newly formed blood vessels [16]. In addition to promoting the production of pro-angiogenic factors, nicotine has been implicated in modulating the activity of endothelial cells directly. Nicotine can induce the proliferation, migration, and tube formation of endothelial cells through the activation of signaling pathways such as the PI3K/Akt and MAPK cascades, further facilitating the process of angiogenesis [17].

Nicotine has also been shown to regulate the expression and activity of matrix metalloproteinases (MMPs), which play crucial roles in the degradation of the extracellular matrix and the remodeling of the tumor microenvironment, creating a permissive environment for angiogenesis. Moreover, the pro-angiogenic effects of nicotine are thought to be mediated, in part, by its ability to induce the expression of hypoxia-inducible factor-1 alpha (HIF-1α), a transcription factor that regulates the expression of various angiogenic genes in response to low oxygen conditions. Nicotine has been shown to stabilize HIF-1α and promote its nuclear translocation, leading to the transcription of target genes involved in angiogenesis, such as VEGF and PDGF.

Table 3: Summary of the effects of nicotine on angiogenesis in OSCC.

Mechanism	**Effects of Nicotine**
Pro-angiogenic Factors	- Upregulates VEGF and VEGFRs - Induces the production of FGF, PDGF, and IL-8
Endothelial Cell Modulation	- Promotes endothelial cell proliferation, migration, and tube formation - Activates PI3K/Akt and MAPK pathways in endothelial cells
Matrix Remodeling	- Regulates the expression and activity of matrix metalloproteinases (MMPs)
Hypoxia Response	- Stabilizes and promotes the nuclear translocation of HIF-1α - Induces the expression of HIF-1α target genes involved in angiogenesis

Nicotine and the Tumor Microenvironment

Cancer-Associated Fibroblasts (CAFs): As mentioned earlier, nicotine can induce the expression of EMT-related transcription factors and the secretion of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in OSCC cells [18]. These factors play crucial roles in the activation and recruitment of CAFs within the TME. Once activated, CAFs can further promote tumor progression through various mechanisms, including the secretion of growth factors, cytokines, and matrix-remodeling enzymes.

Immune Modulation: Nicotine has been shown to exert immunomodulatory effects within the TME, contributing to the evasion of anti-tumor immune responses and the establishment of an immunosuppressive microenvironment. One of the key mechanisms involves the recruitment and activation of immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).

Nicotine can induce the production of cytokines and chemokines that attract and activate Tregs and MDSCs, which in turn suppress the activity of cytotoxic T cells and natural killer (NK) cells, respectively. Additionally, nicotine has been shown to impair the maturation and function of dendritic cells, which are critical for initiating anti-tumor immune responses [19]. Furthermore, nicotine can modulate the expression of immune checkpoint molecules, such as programmed cell death protein 1 (PD-1) and its ligand

PD-L1, on tumor cells and immune cells within the TME. Upregulation of these checkpoint molecules can lead to the suppression of anti-tumor immune responses, contributing to tumor immune evasion and progression.

Extracellular Matrix Remodeling: The extracellular matrix (ECM) is a crucial component of the TME, providing structural support and signaling cues that regulate various cellular processes, including proliferation, migration, and invasion. Nicotine has been implicated in the remodeling of the ECM through its ability to induce the expression and activity of matrix metalloproteinases (MMPs). MMPs are a family of enzymes that degrade various components of the ECM, facilitating cancer cell invasion and metastasis. Nicotine has been shown to upregulate the expression and activity of specific MMPs, such as MMP-2, MMP-9, and MMP-14, in OSCC cells and CAFs. This ECM remodeling can create a permissive environment for tumor cell invasion, angiogenesis, and the recruitment of other cellular components within the TME [20].

Angiogenesis and Hypoxia: As discussed earlier, nicotine can promote angiogenesis within the TME through various mechanisms, including the upregulation of pro-angiogenic factors (e.g., VEGF, FGF, PDGF) and the modulation of endothelial cell behavior. The formation of new blood vessels within the TME can facilitate the delivery of oxygen and nutrients to the rapidly proliferating tumor cells, supporting their growth and survival. However, the rapid expansion of tumor cells often results in regions of hypoxia (low oxygen levels) within the TME [21]. Nicotine has been shown to induce the stabilization and nuclear translocation of the transcription factor HIF-1α, which plays a crucial role in mediating cellular responses to hypoxic conditions. Activation of HIF-1α by nicotine can lead to the transcription of genes involved in angiogenesis, glycolytic metabolism, and survival, further contributing to tumor progression and adaptation to the hypoxic TME.

Therapeutic Implications and Future Directions:

The extensive understanding of the molecular mechanisms through which nicotine contributes to OSCC progression has significant implications for the development of novel therapeutic strategies and preventive measures. Targeting nicotine-mediated signaling pathways, EMT, angiogenesis, and TME modulation may offer promising avenues for improving treatment outcomes and addressing the challenges associated with OSCC.

Targeting Nicotine-Mediated Signaling Pathways: Inhibition of the PI3K/Akt/mTOR, MAPK, and NF-κB pathways, which are activated by nicotine and contribute to OSCC progression, represents a potential therapeutic approach. Several small molecule inhibitors targeting these pathways are currently under investigation or approved for clinical use in various cancers. However, given the complexity and crosstalk between these signaling cascades, a combinatorial approach targeting multiple pathways may be necessary to achieve optimal therapeutic efficacy.

Inhibiting Epithelial-to-Mesenchymal Transition (EMT): Targeting EMT, a process induced by nicotine and associated with increased invasiveness, metastasis, and

therapeutic resistance, is another promising strategy. Inhibitors of EMT-related transcription factors (e.g., Snail, Slug, Twist, and Zeb) or their upstream regulators may hold potential for preventing or reversing the mesenchymal phenotype and associated aggressive behavior of OSCC cells. Anti-Angiogenic Therapies: Given the pro-angiogenic effects of nicotine, anti-angiogenic agents could be explored as potential therapeutic options for OSCC. Several anti-angiogenic drugs targeting VEGF signaling, such as bevacizumab (a monoclonal antibody against VEGF-A), have shown promising results in other cancer types and may be evaluated in combination with standard treatments for OSCC.

Targeting the Tumor Microenvironment: Modulating the tumor microenvironment, which is significantly influenced by nicotine, represents a promising approach for OSCC treatment. Strategies targeting cancer-associated fibroblasts (CAFs), immunosuppressive cells (e.g., Tregs, MDSCs), or immune checkpoint inhibitors could be explored to counteract the immunosuppressive and pro-tumorigenic effects of nicotine within the TME.

Combination Therapies and Personalized Approaches: Given the multifaceted nature of nicotine's effects on OSCC progression, a combinatorial approach targeting multiple pathways and processes may be necessary for optimal therapeutic efficacy. Additionally, personalized treatment strategies based on the molecular profile of individual tumors and their specific nicotine-mediated alterations could be explored to improve treatment outcomes and minimize adverse effects.

Prevention and Smoking Cessation: While therapeutic interventions are crucial for managing OSCC, prevention and smoking cessation remain the most effective approaches to reducing the burden of this disease. Public health initiatives, educational campaigns, and supportive programs aimed at promoting smoking cessation and reducing exposure to nicotine and other tobacco-related carcinogens should be prioritized.

Future Research Directions: Despite the substantial progress made in understanding the role of nicotine in OSCC progression, several areas warrant further investigation. These include elucidating the interplay between nicotine and other tobacco-derived carcinogens, exploring the potential epigenetic modifications induced by nicotine, and investigating the potential involvement of nicotine in cancer stem cell maintenance and therapeutic resistance. Additionally, the development of advanced in vitro and in vivo models that accurately recapitulate the complex interactions between nicotine, OSCC cells, and the tumor microenvironment would greatly enhance our understanding of the mechanisms underlying nicotine-mediated OSCC progression.

Conclusion:

This comprehensive research article has delved into the intricate molecular mechanisms through which nicotine contributes to the progression of oral squamous cell carcinoma (OSCC). By examining various cellular pathways, signaling cascades, and epigenetic

modifications, we have elucidated the multifaceted roles of nicotine in promoting tumor growth, invasion, metastasis, and therapeutic resistance.

The findings presented in this article highlight the pivotal role of nicotine in activating key oncogenic signaling pathways, such as the PI3K/Akt/mTOR, MAPK, and NF-κB cascades, which drive cellular processes implicated in OSCC progression. Furthermore, nicotine has been shown to induce epithelial-to-mesenchymal transition (EMT), facilitating the acquisition of invasive and metastatic properties, and to promote angiogenesis, ensuring a constant supply of oxygen and nutrients to the rapidly proliferating tumor cells [22]. Moreover, this article has explored the profound impact of nicotine on the tumor microenvironment, creating a permissive ecosystem for tumor growth and dissemination. Nicotine has been implicated in the activation and recruitment of cancer-associated fibroblasts (CAFs), the modulation of anti-tumor immune responses, the remodeling of the extracellular matrix, and the adaptation to hypoxic conditions through the stabilization of HIF-1α.
The findings presented in this comprehensive research article have significant implications for the development of novel therapeutic strategies and preventive measures targeting nicotine-mediated OSCC progression [23]. Potential therapeutic approaches include inhibiting nicotine-mediated signaling pathways, targeting EMT, employing anti-angiogenic agents, and modulating the tumor microenvironment through various strategies, such as targeting CAFs, immunosuppressive cells, or immune checkpoint inhibitors. Additionally, this article emphasizes the importance of prevention and smoking cessation as the most effective approaches to reducing the burden of OSCC. Public health initiatives, educational campaigns, and supportive programs aimed at promoting smoking cessation and reducing exposure to nicotine and other tobacco-related carcinogens should be prioritized [24], [25].

Future research directions highlighted in this article include elucidating the interplay between nicotine and other tobacco-derived carcinogens, exploring potential epigenetic modifications induced by nicotine, investigating the involvement of nicotine in cancer stem cell maintenance and therapeutic resistance, and developing advanced in vitro and in vivo models to accurately recapitulate the complex interactions between nicotine, OSCC cells, and the tumor microenvironment.

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