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(REVIEW ARTICLE)

The Effect of Tobacco Exposure on the Human Oral Mucosal Transcriptome

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Abstract

Smoking is one of the main risk factors in the development of various oral health disorders, including oral cancer and periodontal disease. Tobacco smoke exposure not only physically affects the oral mucosa but also triggers significant molecular and genetic changes. Transcriptome, defined as the complete set of RNA transcribed in a cell, serves as an important indicator in understanding the biological impact of tobacco smoke carcinogens on oral epithelial cells. This study aims to identify the content and pathogenesis of tobacco smoke on human oral mucosa, understand the theoretical concept of the oral mucosal transcriptome, and analyze the relationship between the pathophysiology of tobacco smoke exposure and transcriptomic changes in human oral mucosa. This study was conducted using a literature review method, based on previous research found through Google Scholar that discusses the effects of tobacco exposure on the oral mucosal transcriptome. Tobacco smoke exposure has been proven to cause significant dysregulation in gene expression within oral epithelial cells. The disrupted molecular pathways include Wnt signaling, integrin signaling, and Rac protein activity, which are associated with carcinogenesis. Additionally, mutations in the tumor suppressor gene p53 were found in smokers, indicating early signs of cellular transformation toward oral cancer. Smoking has distinct effects on the transcriptome by stimulating inflammatory and oxidative responses. These results indicate that transcriptome analysis can serve as a molecular approach to understanding the pathogenesis of smoking-related oral cavity disorders and provide a foundation for the development of biomarker-based preventive strategies.

Keywords: Tobacco Smoke; Carcinogenic; Oral Mucosa; Transcriptome

1. Introduction

According to data from the World Health Organization, the number of smokers aged over 15 years worldwide has reached 1.1 billion people, with 942 million being men and 175 million women. Of this population, 300 million reside in developed countries, while 800 million live in developing countries. Southeast Asia (ASEAN) contributes 122 million adult smokers, half of whom reside in Indonesia. The number of smokers in Indonesia is approximately 65.2 million, making it the country with the highest prevalence of adult male smokers in ASEAN, recorded at 66% [7].

The function of the oral mucosa is to protect underlying tissues and organs from physical, chemical, mechanical, and microbial threats. Exposure to ingested toxins can alter the structure of the oral epithelium, leading to adaptive/reactive or pathological changes. Tobacco smoke exposure is a known risk factor for oral disease development. Besides increasing the risk for oral cancer, tobacco smoke is also associated with benign mucosal conditions such as periodontal disease and gingivitis. Although smoking does not directly affect the cell cycle in oral keratinocytes, it alters the number of cells showing early and late apoptosis features, indicating an impact on oral epithelial biology [12]. Tobacco smoke is also associated with increased risk of tooth loss, implant failure, oxidative stress, inflammation, and structural changes in mucosal epithelium [13].
Human cancers are characterized by deregulated gene expression involved in critical cellular functions like growth control and differentiation. Tobacco is a major risk factor for various human cancers due to the disruption of genes

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related to carcinogenesis and tissue damage. The oral transcriptome in smokers can be analyzed to determine the effect of tobacco on mucosal cells. Transcriptomic signature analysis has shown differential expression of key cell-type genes [9, 10]. Developing transcriptome-based biomarkers for high-risk smokers may provide a foundation for risk-reduction strategies, including chemoprevention. In general, transcriptomic changes reflect changes in gene expression. The cellular composition of biopsies also influences transcriptome results [2, 11].

2. Material and methods

The method used in this study is a literature review approach. The researchers conducted an analysis based on studies found on Google Scholar that focus on the impact of tobacco smoke exposure on the transcriptome of human oral mucosa. By collecting and evaluating various previous studies, this research aims to identify the carcinogenic effects of tobacco smoke on gene expression and molecular pathways in oral epithelial cells. Through this review, the researchers examined findings related to the dysregulation of gene expression, mutations in the tumor suppressor gene p53, and molecular pathways disrupted in connection with carcinogenesis. This approach allows the researchers to summarize the latest evidence and link various biological and pathological aspects of tobacco smoke exposure to the transcriptome of human oral mucosa.

2.1. Tobacco Acid

Since 1950, the identification of chemical components in tobacco has been conducted. To date, nearly 7,000 chemical compounds have been identified in cigarette smoke. Of these 7,000 compounds, 69 are known to be carcinogenic. Carcinogenic compounds present in cigarette smoke include acetaldehyde, arsenic, benzene, cadmium, ethylene oxide, formaldehyde, and nickel polonium. In addition to nicotine, additives, flavorings, and fragrances are also used in tobacco to cater to consumer (smoker) preferences. Currently, some types of cigarettes are equipped with filters to reduce the levels of tar and nicotine [1]. DNA methylation reflects exposure to various lifestyle factors, including smoking. Several studies have shown a reproducible relationship between tobacco smoking and altered DNA methylation at several cytosine-phosphate-guanine (CpG) sites. Some DNA methylation sites associated with tobacco smoking are also localized in genes related to coronary artery disease and lung disease [4].

Tar and gases from cigarette smoke contain stable oxidants with long half-lives, including semiquinones and carbon-centered free radicals. Additionally, nitric oxide (NO) is involved in carcinogenesis and tumor promotion. Cigarette smoke-induced iNOS causes DNA damage mediated by NO and DNA repair mechanisms. Furthermore, iNOS expression is positively associated with p53 mutations in colon, lung, and oropharyngeal tumors. The interaction between cigarette smoke oxidants and DNA leads to the formation of oxidized DNA bases such as 8-oxo-7,8-dihydroguanine (8-oxoGua) and 8-oxo-2′-deoxyguanosine (8-oxodG). The levels of 8-hydroxydeoxyguanosine (8-OHdG) expression and secretion are higher in smokers compared to non-smokers, both with and without lung cancer. Moreover, the levels of 8-OHdG in BALF are associated with TNM stage according to the malignant tumor TNM classification [3].

2.2. Oral Mucosa Transcriptome

The transcriptome refers to the entire set of RNA synthesized in a specific cell or tissue. It is highly sensitive to changes in the cell/tissue (such as time, type, developmental stage) and the surrounding environment (compounds and carcinogens). The classes of RNA transcribed in eukaryotic cells include messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), and regulatory RNA (regRNA). mRNA is transcribed from protein-coding genes and subsequently translated to encode proteins. rRNA, tRNA, and regRNA are transcribed from non-coding RNA genes, and the transcribed RNA species are functional entities that are not further translated. According to the Ensembl database version 95.38, the human genome contains over 20,000 protein-coding genes, more than 22,000 RNA genes, and over 15,000 pseudogenes, expressing a rich transcriptome with more than two hundred thousand types of gene transcripts. The transcriptome of cancer cells is more complex than that of normal cells. The molecular processes responsible for the abundant transcriptome diversity in tumor cells include alternative splicing, intron retention, alternative promoters, alternative polyadenylation signals, frameshift mutations, point mutations, deletions/insertions in exonic regions, transpositions affecting open reading frames, and RNA editing. rRNA and tRNA, as non-coding RNAs, play important roles during translation; rRNA interacts with proteins to form ribosomal subunits (translation sites), and tRNA interacts with specific ribosomal sites and facilitates amino acid transfer during translation [6].

3. Results and discussion

3.1. Changes in Gene Expression in the Oral Mucosa of Smokers

Smoking significantly alters the transcriptome by activating inflammatory and oxidative responses and modifying gene expression (Khaleel et al., 2022). In oral epithelial cells, smoking induces the expression of genes involved in xenobiotic metabolism and oxidative stress. Increased expression was found in genes such as *CYP1A1*, *CYP1B1*, *AKR1C1/C2*, *UGT1A*, *AHRR*, *ALDH3A1*, *GPX2*, *PTGES*, *ALOX12B*, *ALOX15B*, *CHRNA3*, and *CEACAM7*. Conversely, decreased expression was noted in *CCL18*, *SOX9*, *IGF2BP3*, and *LEPR* [2, 11].

3.2. Disrupted Molecular Pathways in Smokers

Components of cigarette smoke can influence transcriptome changes through chromatin remodeling and DNA methylation in cells. These changes are critical at the level of DNA and specific genes. The use of electronic cigarettes is also believed to have similar harmful effects. The inhaled substances are also classified as toxic and hazardous, especially to the respiratory system, where they can disrupt the oxidative-antioxidative balance (free radicals, irritants). Cigarette smoke can induce molecular-level changes in epithelial cells that result in deregulation of gene expression. Global transcriptome profiling analysis shows deregulation of key genes and molecular pathways in oral epithelial cells. Functional pathway analysis of differentially expressed genes indicates that in both e-cigarette users and smokers, these genes are primarily associated with cancer in the body. The canonical Wnt/Ca+ signaling pathway in e-cigarette users and the non-canonical integrin signaling pathway in smokers are the most disrupted. Research findings indicate that the use of e-cigarettes leads to deregulated expression of key genes and molecular pathways in oral epithelial cells directly exposed to carcinogens [8].

Transcriptome analysis of oral cells from smokers shows deregulation of key genes, most of which converge on cancer-related pathways and functions. The final part of this biological possibility will require decoding the molecular pathways mediated by electronic cigarettes in oral carcinogenesis. The deregulated oral transcriptome of smokers consists of 80% upregulated and 20% downregulated transcripts, compared to the physiological transcriptome of non-smokers. According to comparative computational analysis of transcriptomic abnormalities commonly observed in the oral mucosa of smokers versus non-smokers, the main altered pathways in smokers include keratinocyte differentiation, cell-cell adhesion, signaling routes involving integrins, the Rho small GTPase superfamily, and serine/threonine phosphatase activity. The key pathways altered in exposed oral mucosa involve Wnt-binding proteins, the Rho small GTPase superfamily, ATP-binding proteins, chaperones, and stress responses [6].

Rac proteins have multiple regulatory functions in transcription, cytoskeleton organization, apoptosis, cell proliferation, and cell migration. Overexpressed and mutated Rac proteins surpass normal regulatory signaling pathways, allowing affected cells to evade apoptosis and thereby initiate uncontrolled cell proliferation and carcinogenesis. The transcriptome of peripheral blood mononuclear cells from smokers differs significantly from that of non-smokers, with modulations observed in immune-related pathways. Compared to non-smokers, the oral mucosa of smokers shows deregulated expression of many protein-coding genes that disrupt oral homeostasis. Tobacco smoke alters the expression of genes involved in the following pathways: nicotine signaling (*CHRNA3* ↑), xenobiotic metabolism (*AHRR* ↑, *AKR1C1/C2* ↑, *CYP1A1* ↑, *CYP1B1* ↑, *UGT1A* ↑), oxidative stress (*ALDH3A1* ↑, *GPX2* ↑), eicosanoid synthesis (*PTGES* ↑, *ALOX12B* ↑, *ALOX15B* ↑), and cell adhesion (*CEACAM7* ↑), as well as humoral and cellular immune responses (*CCL18* ↓), mRNA binding, protection and cytosolic translocation (*IGF2BP3* ↓), cell differentiation (*SOX9* ↓), and cell signaling with cell-mediated immune responses (*LEPR* ↓) [6].

3.3. Gene Mutations and Their Relationship with Oral Carcinogenesis

Tobacco smokers have a higher number of mutations in a critical tumor suppressor gene known as *p53*. Mutations in the *p53* gene can result from DNA damage caused by tobacco smoke carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and nitrosamines. *p53* mutations and expression aberrations are among the early events leading to oral carcinogenesis. Overexpression of *p53* is associated with precancerous lesions and oral cancer. The canonical transcript of *p53* encodes the full-length protein (393 amino acids), which functions as a transcription factor regulating apoptosis, DNA repair, the cell cycle, and cell differentiation. Non-canonical transcripts of *p53* encode isoforms associated with malignant lesions, indicating a tumor-promoting role (in contrast to the canonical isoform). According to Ensemble, the *p53* gene has more than twenty non-canonical protein-coding transcript variants, which may have roles in either promoting or suppressing tumors; experimental efforts are required to uncover their specific functions. *Surviving*, a target gene of canonical *p53* protein, encodes a protein that functions as an inhibitor of apoptosis proteins (IAP), and it has six transcript variants that are overexpressed in oral cancers and correlate with tumor stage [6].

4. Conclusion

Smoking has distinct effects on the transcriptome as it stimulates inflammatory and oxidative responses and alters gene expression across various tissue types. In oral epithelial cells, smoking increases the expression of genes involved in xenobiotic metabolism and redox stress. The global transcriptome in oral epithelial cells reveals dysregulation of key genes and biochemical pathways. Transcriptome analysis of oral cells in smokers shows deregulation of critical genes, most of which are involved in cancer-related pathways and activities. Tobacco users exhibit a higher number of mutations in the tumor suppressor gene *p53*. Mutations in the *p53* gene can develop as a result of DNA damage caused by carcinogens found in tobacco smoke, such as polycyclic aromatic hydrocarbons (PAHs) and nitrosamines. *p53* mutations and expression aberrations are among the early events that lead to carcinogenesis in the oral cavity.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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