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Research Article

An Insight into Cellular and Molecular Changes Associated with Cigarette Smoking.

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Abstract

Cigarette smoking presents a significant global health challenge, with approximately 8 million deaths attributed annually to tobacco use. The intricate chemical composition of cigarettes, containing over 5,000 harmful substances like nicotine and tar, disrupts cellular functions, fostering chronic inflammation and immune dysregulation. This not only damages the lungs but also weakens systemic immunity, heightening susceptibility to infections and exacerbating autoimmune diseases and oral health issues. This review provides an overview of the profound cellular changes induced by cigarette smoking, emphasizing its impact on respiratory and cardiovascular health, along with alterations in gene expression profiles across various tissues and cell types. Structural degradation of the airways compromised mucociliary clearance, and heightened inflammation in the lungs are notable effects. Additionally, smoking significantly contributes to the development and progression of various cardiovascular diseases. Understanding the genetic alterations triggered by tobacco exposure and exploring signaling cascades in tobacco-related diseases are crucial for devising effective interventions. Further research, including transcriptome studies on the effects of smokeless tobacco, is essential to address these challenges and pave the way for targeted interventions against tobacco-related diseases.

INTRODUCTION

Cigarette smoking imposes a significant global health burden, with the WHO attributing around 8 million deaths annually to tobacco use—7 million from direct smoking and 1.2 million from secondhand smoke [1]. The harmful effects of smoking stem from its complex chemical composition, which includes over 5,000 harmful substances like nicotine, tar, and carbon monoxide. These chemicals disrupt cellular functions, causing chronic inflammation and altering immune responses, which can either hyperactivate or suppress the immune system based on exposure levels and tobacco type. This not only damages the lungs but also weakens systemic immunity, increasing susceptibility to infections and worsening autoimmune diseases and oral health issues [2, 3].

To tackle this public health challenge, a comprehensive approach is necessary, emphasizing the evaluation and enhancement of smoking cessation programs to improve quit rates and long-term abstinence. Developing tailored interventions that address individual needs and incorporating technological advancements can enhance the effectiveness and reach of these programs [1]. Traditional cessation methods like counseling and nicotine replacement therapy must be supplemented with innovative approaches, such as digital health tools and personalized medicine, to address the diverse needs of smokers. By leveraging technology, we can provide more accessible and customizable support, increasing the likelihood of successful quitting [2,3].

Furthermore, public health policies play a critical role in reducing smoking rates. Measures such as increasing tobacco taxes, implementing strict advertising bans, and creating smoke-free environments have proven effective in decreasing smoking prevalence. Education campaigns that highlight the dangers of smoking and promote cessation resources are also crucial in changing public attitudes and behaviors toward tobacco use [3,4].

This review aims to highlight the complex effects of smoking and the urgent need for evidence-based cessation strategies, aiming for improved global health outcomes by understanding and mitigating smoking-induced pathologies. By prioritizing research into the molecular and cellular mechanisms of smoking-related damage, we can develop more targeted treatments and preventive measures. Ultimately, a multifaceted approach combining cessation support, policy interventions, and scientific research is essential to combat the global smoking epidemic and improve public health.

CELLULAR CHANGES IN CIGARETTE SMOKING

Cigarette smoking induces profound cellular changes due to its complex chemical composition, which includes over 5,000 harmful substances like nicotine, tar, and carbon monoxide. These chemicals cause chronic inflammation and oxidative stress,

leading to DNA damage and mutations. Nicotine affects neurotransmitter release, while tar and other carcinogens disrupt cellular homeostasis, promoting uncontrolled cell growth and cancer [5]. Smoking also impairs immune function, either hyperactivating or suppressing the immune response, depending on exposure levels. This dysregulation increases susceptibility to infections, exacerbates autoimmune diseases, and contributes to the development of chronic conditions such as cardiovascular diseases and chronic obstructive pulmonary disease (COPD) [6].

Additionally, smoking impacts cellular signaling pathways and alters gene expression, leading to detrimental effects on cell function and survival. It disrupts the balance between pro-inflammatory and anti-inflammatory cytokines, further aggravating inflammatory responses [7]. The harmful substances in cigarette smoke also induce cellular senescence and apoptosis, accelerating tissue damage and aging. Moreover, endothelial cell dysfunction caused by smoking contributes to vascular damage and atherosclerosis, increasing the risk of cardiovascular events. These widespread cellular changes underscore the extensive damage smoking inflicts on the body, highlighting the urgent need for effective smoking cessation strategies to mitigate these harmful effects [8,9].

Pulmonary changes in Cigarette smoking.

Cigarette smoking inflicts extensive damage on the respiratory epithelium, disrupting crucial cellular functions and sparking inflammation. This harm includes structural degradation of the airway lining, hampered mucociliary clearance, and increased inflammation [1]. Chronic exposure to cigarette smoke leads to cellular injury, the loss of ciliated cells, and disruption of epithelial integrity, exacerbating structural damage to the airway lining [2]. The respiratory epithelium, equipped with cilia that normally expel mucus and debris from the airways, suffers impaired function due to cigarette smoke, compromising the mucociliary escalator and fostering mucus and debris buildup, heightening susceptibility to infections and inflammation [3,4].

Inhaling cigarette smoke initiates an inflammatory cascade in the lungs, involving the recruitment and activation of immune cells such as macrophages, neutrophils, and lymphocytes [10]. Macrophages release pro-inflammatory cytokines and reactive oxygen species (ROS), fueling inflammation and tissue damage. Neutrophils invade the airways in response to smoke-induced injury, releasing proteases that further damage tissues. Lymphocytes, including CD4 and CD8 T cells, activated by cigarette smoke antigens, churn out inflammatory mediators, kickstarting adaptive immune responses [11].

Cigarette smoke also alters inflammatory responses generated by respiratory epithelial cells, suppressing antiviral immunity and impeding the phagocytic activity of alveolar macrophages [11]. This ineffectiveness leads to compromised bacterial clearance, impaired phagocytosis of apoptotic bronchial epithelial cells, and defective efferocytosis.

Consequently, apoptotic cell contents spill into surrounding tissue, exposing neighboring cells to enzymes and oxidants. Accumulated apoptotic cells may undergo secondary necrosis, perpetuating inflammation and leading to abnormal accumulation of apoptotic epithelial cells in the airway lumen [11,12].

These cumulative cellular alterations contribute to the development of chronic obstructive pulmonary disease (COPD) and lung cancer [13]. COPD manifests as airflow limitation, chronic inflammation, and irreversible lung damage, with cigarette smoke as the primary risk factor. Lung cancer results from the malignant transformation of respiratory epithelial cells, driven by the carcinogens present in cigarette smoke [12,13].

Cigarette smoke disrupts mucociliary clearance by decreasing ciliary beating and increasing mucus production, allowing deeper penetration of toxins and infectious agents [14]. Epithelial to mesenchymal transition (EMT), associated with redox imbalance and oxidative stress, thickens and remodels airway walls, obstructing airways. Alveolar EMT disrupts re-epithelialization and contributes to emphysema development. EMT enhances fibroblast migratory capacity, invasiveness, resistance to apoptosis, and extracellular matrix (ECM) component production [13,14].

Furthermore, cigarette smoking prompts immune dysfunction, with heightened responsiveness of epithelial and innate immune cells to cigarette derivatives [14]. Oxidative stress triggers inflammatory response-related transcription factors such as NF-kB and AP-1. Activation of these factors by cigarette smoke extract (CSE) promotes the production of proinflammatory mediators and chemokines, driving sustained immune cell recruitment and activation. This hyperinflammatory state exacerbates reactivity to inhaled antigens, tissue damage, and remodeling [15]. Despite hyperactivation, innate and adaptive immune responses are dysfunctional, with constitutively activated inflammation pathways associated with reduced responses to acute infections. Immune responses to viral antigens are notably diminished, as cigarette smoke dampens Toll-like receptor (TLR) 3-mediated responses to double-stranded RNA [15,16].

Cigarette smoke-induced oxidative stress diminishes the phagocytic activity of alveolar macrophages, resulting in pathogen and debris accumulation in the lungs, exacerbating inflammation and lung injury [15]. This scenario significantly influences the development and progression of respiratory diseases, including COPD and lung cancer [16].

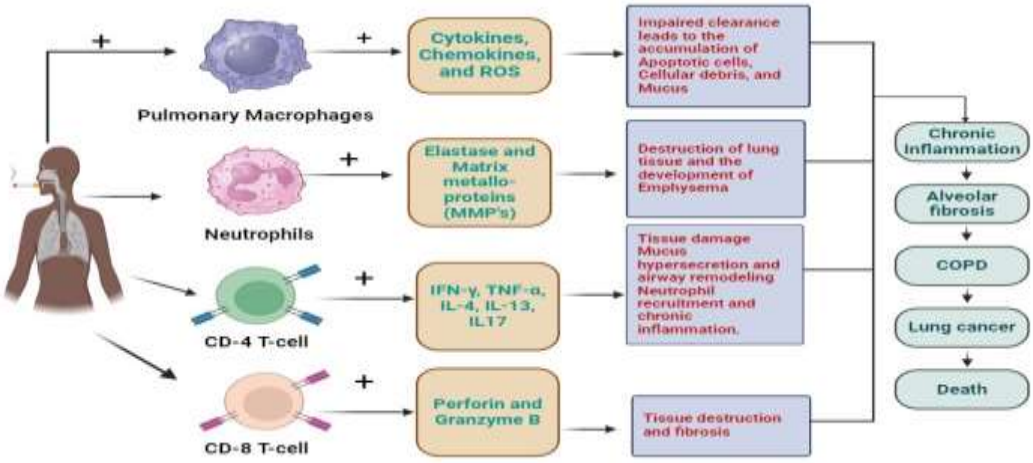

Fig 1: Inflammatory changes in lungs due to Cigarette smoking.

Cardiovascular changes due to Cigarette smoking.

Cigarette smoking exerts a profound and multifaceted impact on cardiovascular health, setting in motion a complex cascade of cellular changes that contribute significantly to the development and progression of various cardiovascular diseases (CVDs) [15]. Among the noxious constituents of cigarette smoke, nicotine stands out for its pivotal role in eliciting a spectrum of responses within the cardiovascular system, culminating in a broad array of pathological manifestations [16].

The endothelium, serving as a pivotal interface between the circulatory system and the vascular wall, emerges as a primary target of the deleterious effects induced by cigarette smoke exposure [16]. Upon encountering cigarette smoke, endothelial cells respond by releasing a milieu of inflammatory mediators, including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), initiating a pro-inflammatory cascade that not only promotes the recruitment of leukocytes but also sets the stage for the initiation and progression of atherosclerosis [16,17].

Central to vascular homeostasis is the role played by nitric oxide (NO), a potent vasodilator synthesized by endothelial nitric oxide synthase (eNOS) [17]. However, cigarette smoke-induced oxidative stress wreaks havoc on this delicate balance, impairing eNOS function and leading to a diminished bioavailability of NO, consequently

compromising endothelium-dependent vasodilation [17,18].

Nicotine, a prominent component of cigarette smoke, orchestrates a multifaceted signaling cascade upon activation of nicotinic acetylcholine receptors (nAChRs), thereby exerting a profound influence on cardiovascular physiology and pathology [17]. This cascade, initiated by nicotine, ultimately culminates in the activation of protein kinase C (PKC) and the subsequent production of ROS, setting the stage for the activation of nuclear factor-κB (NF-κB), a transcription factor implicated in the expression of pro-inflammatory genes [18].

Furthermore, nicotine-mediated activation of nAChRs precipitates the release of vasoconstrictors, such as endothelin-1, while concurrently inhibiting the action of vasodilators, including NO [17,18]. This dysregulation in vascular tone modulation serves to promote vasoconstriction and elevate blood pressure, thereby subjecting the vascular wall to undue stress and fostering an environment conducive to the development and progression of atherosclerosis and other CVDs [18].

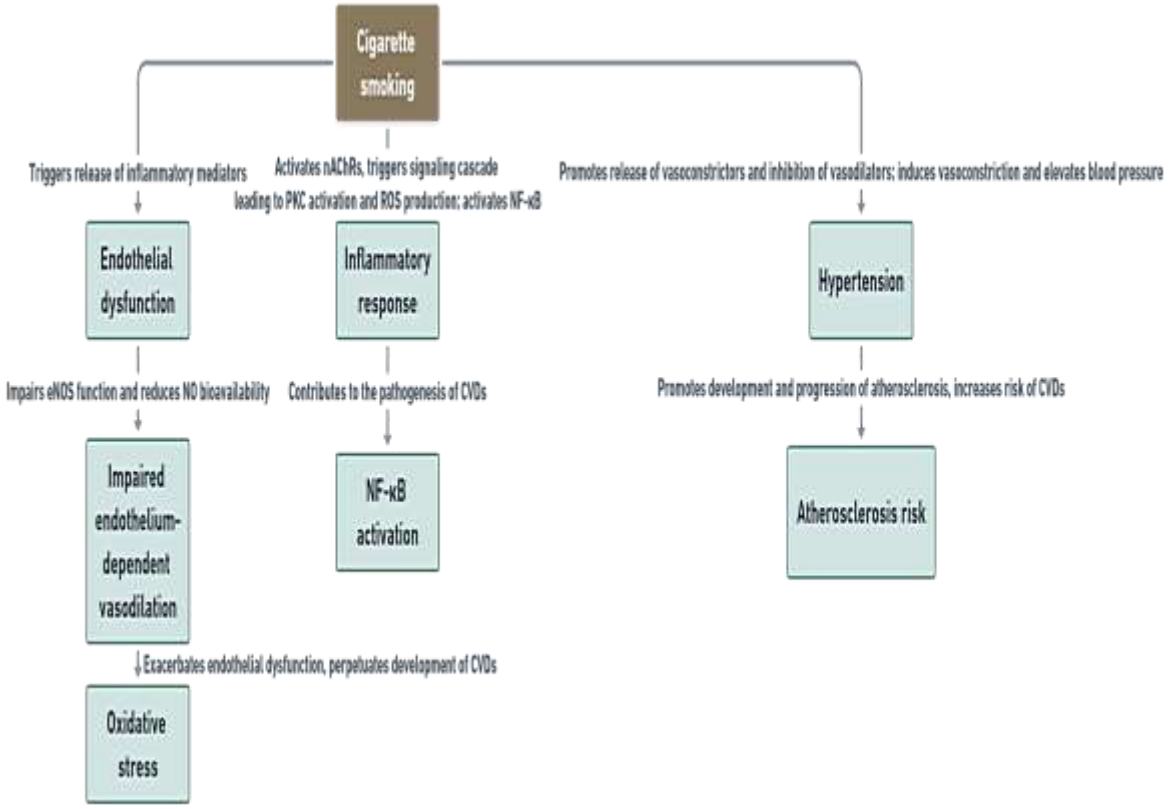

Fig 2: Inflammatory changes in Cardiovascular system due to Cigarette smoking.

MOLECULAR CHANGES IN CIGARETTE SMOKING

Exposure to cigarette smoke leads to significant alterations in gene expression profiles across various tissues and cell types, with profound implications for the development and progression of tobacco-related diseases such as cancer, cardiovascular disease, and chronic obstructive pulmonary disease (COPD) [19]. One example is the upregulation of IL6R mRNA levels in bronchial epithelial cells, associated with increased susceptibility to respiratory infections and chronic inflammation. Interestingly, specific IL6R haplotypes have been linked to COPD risk [20].

Cigarette smoke exposure also affects pseudogene expression, with instances of both upregulation and downregulation observed in smoker buccal mucosa. Notably, some pseudogenes, like FMO6P, exhibit sequence homology with genes involved in nicotine metabolism, while others, such as ALDOAP2 and PNLIPRP2, are implicated in various physiological processes [20,21]. Additionally, analysis of upstream regulators highlighted the significant differential regulation of the TP53 gene in smoker buccal mucosa, with known implications for cellular proliferation and cancer development [21].

The complex composition of cigarette smoke, comprising over 5000 chemicals, including

numerous carcinogens, disrupts biological pathways related to cellular proliferation, inflammation, and tissue injury, thereby fostering carcinogenesis [21]. Carcinogens like polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes induce DNA damage, oxidative stress, and inflammation, promoting genetic and epigenetic alterations conducive to cancer development [22,23]. Moreover, cigarette smoke carcinogens can induce epigenetic modifications, including DNA methylation changes and histone modifications, which further contribute to cancer pathogenesis [24].

Recent investigations have revealed associations between smoking-related CpGs and gene expression probes, underscoring the intricate molecular interplay induced by cigarette smoking [25]. These findings collectively highlight the broad spectrum of molecular changes induced by cigarette smoke, encompassing gene expression alterations and epigenetic modifications, and their pivotal role in the pathogenesis of various diseases, including cancer, cardiovascular disease, and COPD.

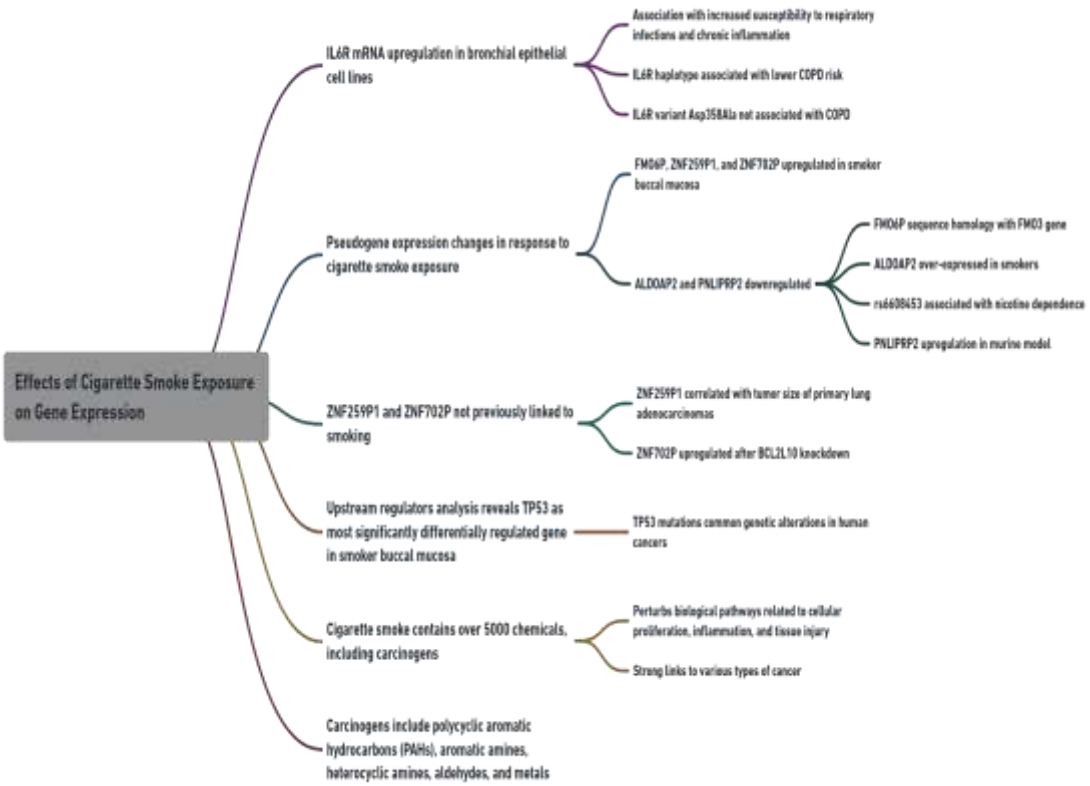

Fig 3: Alterations in gene expression and epigenetic modification due to cigarette smoking

FUTURE DIRECTIONS

Extensive research on the cellular and molecular changes due to cigarette smoking has revealed key insights into how genetic, epigenetic, and environmental factors contribute to disease pathogenesis. Notably, mutations in genes like TP53, KRAS, and EGFR, along with epigenetic modifications in genes such as CDKN2A and RASSF1, are linked to smoking-induced cancers. However, gaps remain in our understanding, particularly regarding the impact of smokeless tobacco on gene expression. Studies indicate smokeless tobacco affects genes involved in immune response, metabolism, and DNA repair, but further research is needed. Developing accurate cellular models of chronic tobacco exposure could enhance our understanding of these oncogenic mechanisms. Whole exome sequencing of tissues exposed to tobacco may reveal novel mutations and pathways, aiding in personalized medicine approaches and early detection biomarkers for tobacco-related diseases. Investigating the role of signaling proteins like COX-2 and aryl hydrocarbon receptors in tobacco exposure could lead to targeted therapies, given COX-2's role in inflammation and cancer progression.

Transcriptome studies show smokeless tobacco alters gene expression in oral epithelia, affecting cell cycle regulation and cell adhesion, and contributing to inflammation and apoptosis. These insights could guide targeted interventions for oral cancer and other related diseases. A comprehensive approach that integrates genetic, epigenetic, and environmental factors is crucial for understanding tobacco-induced cellular changes and developing effective interventions. Addressing these gaps through continued research will improve prevention, early detection, and treatment strategies for tobacco-related diseases.

CONCLUSION

Cigarette smoking induces intricate cellular and molecular changes, impacting gene expression, epigenetics, and signaling pathways, contributing to respiratory and cardiovascular diseases. Understanding these mechanisms is vital for developing precise interventions to mitigate tobacco's health effects and improve public health globally. However, there are ongoing debates and controversies regarding the extent of genetic vs. environmental influences, the variability of individual responses to tobacco exposure, and the best approaches for treatment and prevention. Exploring the interplay of cigarette smoke-induced alterations at cellular and molecular levels is key to advancing evidence-based strategies against tobacco-related health challenges. This includes addressing controversies about the most effective use of current knowledge and the ethical considerations in tobacco research and public health policies. By resolving these debates, we can better harness scientific insights to develop targeted therapies, inform policy, and ultimately reduce the global burden of tobacco-related diseases.

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