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Toxico-Epigenomic Mechanisms of Smoking Exposure in Lung Cancer Development

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ABSTRACT

Lung cancer remains one of the leading causes of cancer-related mortality worldwide, with cigarette smoking recognized as the primary environmental risk factor contributing to its development. Tobacco smoke contains various carcinogenic compounds that induce oxidative stress and epigenetic alterations, including DNA methylation and histone modifications, which regulate gene expression without altering the DNA sequence. This review aimed to examine the toxico-epigenomic mechanisms underlying smoking-induced lung carcinogenesis, particularly the roles of nicotine-derived nitrosamine ketone (NNK), carbon monoxide, DNA methyltransferases (DNMTs), and chromatin modifications. This study employed a narrative literature review approach by analyzing relevant peer-reviewed scientific publications focusing on tobacco toxicology, epigenetic regulation, and lung cancer mechanisms. The findings indicated that NNK contributes to lung carcinogenesis through DNMT1 stabilization, promoter hypermethylation, and the silencing of tumor suppressor genes, while carbon monoxide promotes hypoxia and reactive oxygen species generation, further enhancing epigenetic dysregulation. These mechanisms influence critical biological processes, including cell proliferation, apoptosis, DNA repair, and tumor progression. Understanding smoking-related epigenetic alterations provides important insights for developing early diagnostic biomarkers and targeted therapeutic strategies, including DNMT inhibitors such as 5-azacitidine, 5-aza-2′-deoxycytidine, and zebularine. This review highlights the importance of integrating toxico-epigenomic approaches to improve understanding and management of smoking-related lung cancer.

INTRODUCTION

Cancer remains a major global health challenge characterized by uncontrolled cellular proliferation, abnormal tissue growth, and the ability to invade surrounding tissues through metastasis. Among various cancer types, lung cancer represents one of the most serious malignancies due to its high incidence and mortality worldwide. The development of lung cancer is influenced by multiple factors, including genetic susceptibility, environmental exposure, lifestyle factors, and, particularly, tobacco smoking. Cigarette smoke contains numerous carcinogenic compounds that can induce molecular alterations in lung cells, leading to disruptions in normal cellular regulation. Therefore, understanding the molecular mechanisms underlying smoking-induced lung cancer development is essential for improving prevention strategies, early detection, and therapeutic approaches.

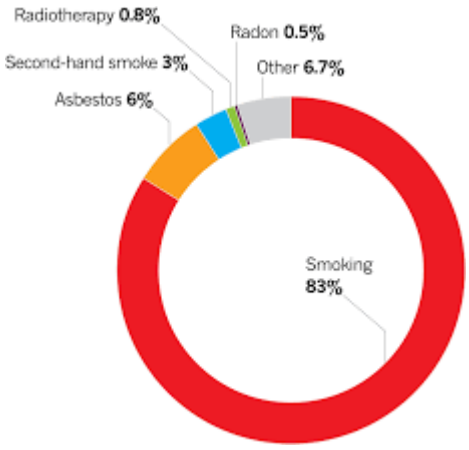

Figure 1. Type of factors causing cancer in the lung (Alex Jackson, 2014)
Source: Jackson (2014).

Cancer development is influenced by multiple factors, including tobacco smoking, diet, physical activity, radiation exposure (e.g., ultraviolet radiation), and infections.

Recent advances in molecular oncology have demonstrated that cancer development is associated not only with genetic mutations but also with epigenetic alterations that regulate gene activity without modifying the DNA sequence. Epigenetic mechanisms, including DNA methylation and histone modification, play essential roles in regulating chromatin structure, transcriptional activity, and cellular differentiation. Environmental factors, such as cigarette smoke exposure, can disrupt these regulatory mechanisms by altering the activity of epigenetic enzymes and modifying gene expression patterns. Consequently, toxico-epigenomics has emerged as an important research field investigating how chemical exposures influence epigenetic regulation and contribute to disease progression, including smoking-related lung cancer.

Although the relationship between cigarette smoking and lung cancer has been extensively established, the precise molecular pathways connecting tobacco-derived chemicals with epigenetic dysregulation require further investigation. Previous studies have demonstrated that nicotine-derived nitrosamine ketone (NNK) can promote carcinogenesis by increasing DNMT1 stability and inducing hypermethylation of tumor suppressor genes. In addition, carbon monoxide exposure from cigarette smoke contributes to hypoxic conditions and oxidative stress, which may enhance abnormal epigenetic regulation. However, existing studies often discuss genetic mutations, toxic compounds, and epigenetic mechanisms separately, creating a research gap regarding the integrated toxico-epigenomic pathway linking smoking exposure to lung cancer development.

DNA methylation can regulate chromatin status and influence gene expression patterns. Tobacco smoking has been identified as the primary preventable cause of lung cancer, with its carcinogenic effects established through extensive epidemiological evidence since the mid-20th century (Jyoti et al., 2016). The causal relationship between smoking and lung cancer was further recognized through the U.S. Surgeon General's reports, which clarified the epidemiological evidence linking tobacco use with cancer risk (Blackadar, 2016). Subsequent research has continued to identify and characterize the chemical components of cigarette smoke and their biological effects (Parascandola, 2004).

Lung cancer generally originates from epithelial cells of the lungs and is classified into two major groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC is characterized by rapid progression and aggressive behavior, whereas NSCLC represents the majority of lung cancer cases, accounting for approximately 85% of diagnoses. NSCLC consists of three major subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Among these subtypes, adenocarcinoma is the most common, followed by squamous cell carcinoma and large cell carcinoma (Charles et al., 2011).

Current knowledge regarding smoking-related lung cancer has primarily focused on either carcinogenic compounds or individual epigenetic mechanisms. Although previous studies have described the roles of DNA methylation, histone modification, and DNMT regulation, limited reviews have integrated the toxicological effects of cigarette-derived compounds with epigenetic alterations at the molecular level. This limitation highlights the need for a comprehensive toxico-epigenomic perspective that explains how specific tobacco components initiate molecular changes and contribute to tumor formation. Therefore, this review provides an integrated analysis of smoking-induced epigenetic dysregulation by connecting chemical exposure, molecular mechanisms, and potential therapeutic implications.

The urgency of studying smoking-related toxico-epigenomic mechanisms is associated with the continued global burden of lung cancer and the challenges of early detection. Many lung cancer cases are diagnosed at advanced stages due to limited availability of effective early biomarkers. Epigenetic alterations are considered promising molecular indicators because they are reversible and may reflect early biological responses to carcinogenic exposure. Understanding tobacco-induced epigenetic changes may contribute to the identification of potential diagnostic biomarkers and the development of targeted therapies aimed at restoring abnormal gene regulation.

This review focuses specifically on two major tobacco-derived compounds, nicotine-derived nitrosamine ketone (NNK) and carbon monoxide, because both demonstrate significant biological effects related to lung carcinogenesis. NNK has been reported to influence DNMT1 regulation and promote abnormal DNA methylation patterns, whereas carbon monoxide contributes to hypoxia and oxidative stress that may further disrupt epigenetic stability. By examining these mechanisms together, this study aims to provide a broader understanding of how smoking exposure contributes to lung cancer development through epigenetic pathways.

The novelty of this review lies in its integrated discussion of toxicological and epigenetic mechanisms associated with smoking-induced lung cancer. Unlike studies that examine genetic mutations, individual carcinogens, or epigenetic alterations separately, this review combines the effects of tobacco chemicals, epigenetic enzyme regulation, chromatin modification, and therapeutic opportunities into a unified framework. This approach provides a more comprehensive explanation of the molecular pathway through which cigarette exposure contributes to malignant transformation.

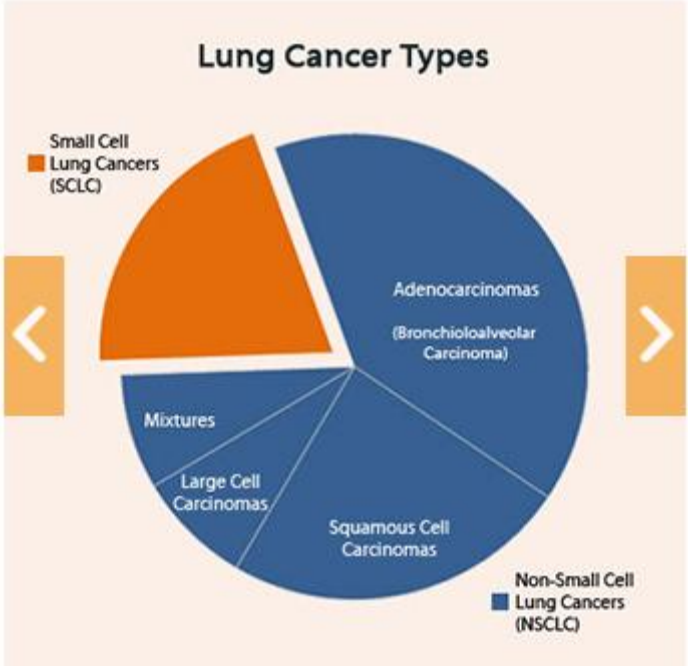

Figure 2. The diagram of lung cancer type in worldwide (Asbestos, 2016)
Source: Asbestos.com (2016).

In many countries, tobacco smoking remains one of the leading causes of lung cancer. Tobacco exposure contributes substantially to cancer-related mortality, particularly among male populations, due to long-term smoking behavior and cumulative carcinogenic exposure (Farhad et al., 2015).

Currently, China is one of the countries with the highest levels of tobacco production and consumption worldwide. The country produces and consumes a substantial number of cigarettes annually, with smoking prevalence remaining high, particularly among males. Approximately 67% of male and 4% of female individuals aged over 15 years in China are reported to be smokers (Zhang et al., 2003).

The objective of this study was to review current scientific evidence regarding the toxico-epigenomic mechanisms involved in smoking-related lung cancer development. Specifically, this review examined the roles of DNA methylation, histone modification, NNK-induced DNMT1 regulation, carbon monoxide-mediated oxidative stress, and potential epigenetic therapeutic strategies. The findings are expected to contribute to a better understanding of the molecular pathways underlying smoking-related carcinogenesis and provide insights for future research focusing on biomarker discovery and targeted treatment development.

METHOD

This study employed a narrative literature review design to examine the toxico-epigenomic mechanisms underlying smoking-related lung cancer development. The reviewed literature consisted of peer-reviewed publications addressing tobacco exposure, carcinogenic compounds, epigenetic regulation, DNA methylation, histone modification, DNA methyltransferases (DNMTs), and lung cancer progression. Relevant studies were selected purposively based on their relevance, scientific quality, and contribution to understanding the molecular mechanisms associated with smoking-induced epigenetic alterations.

The literature review process was supported by a review matrix to systematically extract key information from selected studies, including publication characteristics, research focus, molecular mechanisms examined, and major findings. The credibility of the findings was maintained by prioritizing peer-reviewed sources with clear methodological descriptions and comparing evidence across multiple studies. Data collection involved identifying, screening, evaluating, and synthesizing relevant literature on the relationship between cigarette-derived compounds, epigenetic dysregulation, and lung carcinogenesis.

The collected data were analyzed descriptively through comparison and integration of previous research findings related to DNA methylation, histone modification, NNK-induced DNMT1 regulation, carbon monoxide-mediated oxidative stress, and potential epigenetic therapeutic approaches. The synthesis was conducted to identify consistent patterns and explain the molecular pathways through which smoking exposure contributes to epigenetic alterations and lung cancer development.

RESULTS AND DISCUSSION

Epigenetic Modifications

Epigenetic deregulation impacts a few parts of tumour cell biology such as cell cycle control, cell growth, DNA repair, cell death, and differentiation. The regulation of this modifies the expression of the gene in the absence of the changing of DNA sequences. (Hirota, 2018) Nowadays, rather than the changing of DNA, scientists prefer to use epigenetic modifications such as histone modification and DNA methylation in research. (Diane, 2011) In fact, the rises of the strong possibility of the reversing deregulation of epigenetic mechanisms can be the strategy of treatment for cancer. This strategy can either target or separate the specific perturbations in the epigenetic mechanisms. (Kappi *et al*,2005)

DNA Methylation

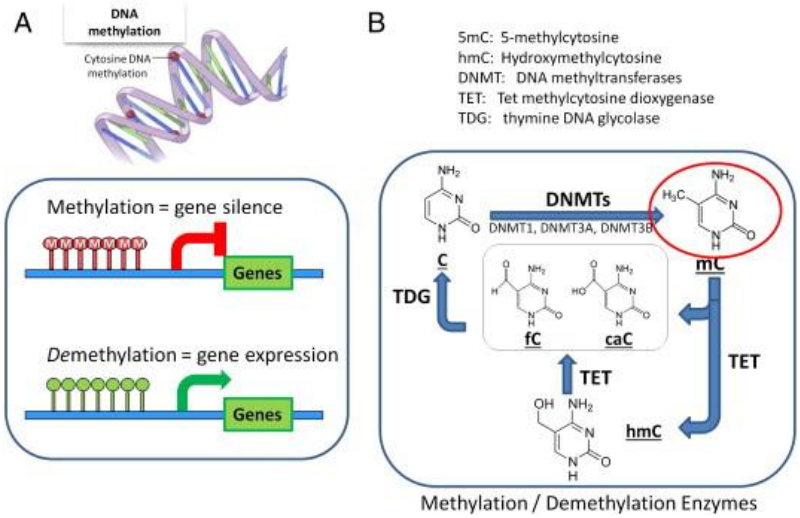

Figure 3. DNA metyhlation and demethylation (Peter, 2014)

Source: Peter (2014).

DNA methylation is where the methyl group from methyl donor SAM (S-adenosylmethionine) is added to a cytosine base within DNA. The members of DNMTs (DNA

methyltransferase) family do the catalyzation in this reaction, which is DNMT1, DNMT2, and DNMT3. (Tong *et al*, 2017) Hence, DNA methylation in promoter sequences along with other marks of chromatin (for example histone modifications) can be used to alter gene activity. The gene could be silenced or expressed as it depends on the modification of the epigenetic pattern. (Abhimanyu *et al*, 2012)

DNA methylation normally is occurred by the transference of the methyl group to CpG or Cytosine-Guanine Dinucleotide. This helps different proteins that ban the entrance of RNA polymerase to bind and silence the active gene. (Philibert *et al*, 2014) DNA methylation is at the 5 positions of cytosine in CpG dinucleotides as it replaces the hydrogen atom with the methyl group but not interfering the CpG islands. (Moore, 2012)

Histone modification

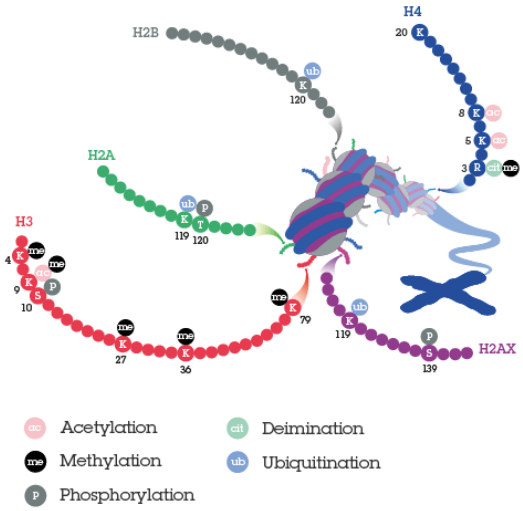

Figure 4. Histone modification (Abcam, 1998)
Source: Abcam (1998).

Histone modification is one of the major examples of a DNA mechanism. (Jenuwein et al, 2001) The histone is wrapped by DNA forming nucleosomal core particles. The histone proteins have N-terminal tails that were created in the nucleosome. Remaining part in these tails are modified affecting the process of chromatin compaction, transcription, and nucleosome dynamics.

In diversity to the present of chromatin compaction, transcription and nucleosome dynamics, the modification of the histones has not uncharacterized fully until now even though some of them are analyzed detailly. (Lawrence et al, 2016)

Therefore, relating to the various histone modification detection, the deeper knowledge about the processes of epigenetic regulation and histone-modifying enzyme targeted drugs has been developed.

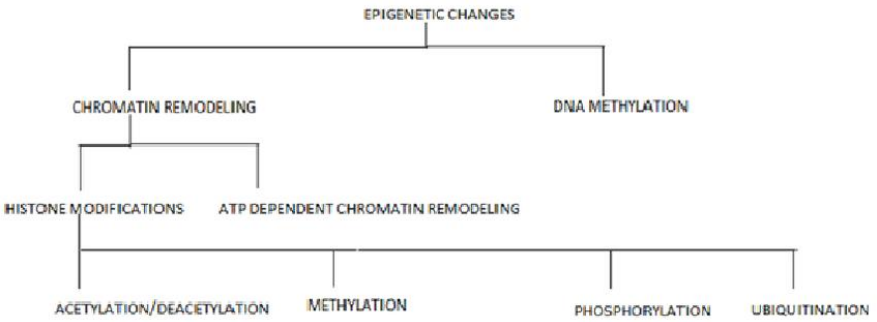

Figure 5. Mechanisms of Epigenetic changes (Abhimanyu et al, 2012)
Source: Abhimanyu et al. (2012).

As mentioned in Figure 5, several types of epigenetic modifications of histone proteins are acetylation, ubiquitination, phosphorylation, and methylation. (Handy *et al*, 2012). All of these are used for the regulation of the genome through the transformation of the local structural dynamics of chromatin. This interaction establishes the landscape of epigenetic changes that arrange the methods of the manifestation of the genome by itself in the variant of developmental stages, cell types, and disease condition such as cancer. (Shihkar *et al*, 2010)

Acetylation/ Deacetylation

Histone acetylation happens at the lysine and arginine residues (Bannister, 2011) Histone acetyltransferases or HAT and histone deacetylases or HDACs mediate the histone acetylation. (Grozinger *et al*, 2002) The HAT activates the gene expression that requires the lysin specifically in the tails of histone. It will be seen as the positive charge transference on the histone and lead to the reduction of the histone affinity that causes DNA structure relaxation and transcription enhancement. (Huyn *et al*, 2017) Histone Acetylation and demethylated DNA are associated. The association of both can appear as local and not spread by the side of DNA. (Irvine *et al*, 2002)

Methylation/Demethylation

Histone methylation is specific to arginine and lysine residues. It starts where the HMTs (Histone Methyltransferases) brings around one to three methyl groups from S-adenosyl-L-methionine to lysine or arginine. (Whestine et al, 2010)

On the other hand, Histone Demethylation removes the methyl groups in histone protein which is done by histone demethylases. Histone demethylases have been found that they involve in the progress of oncogenic or another disease. (Erler, 2014)

Furthermore, HDMs (Histone Demethylases) has a few types. For examples are Jumonji-C domain-containing histone demethylases (JMCs), peptidyl arginine deiminase (PADI), and LSD or lysine-specific demethylases. All these methylation-demethylation events lead to activating or repressing the transcription that depends on the target sites. The location where the methylation has occurred is necessary to establish the effect on the transcription of the gene. (Jin, 2013)

Epigenomic Changes in Lung Cancer

Lung cancer may be initiated and progressed through dynamically genetic that communicate with the epigenetic elements. Nonetheless, the mechanisms of the development and the progression of lung cancer are still unclear. (Shi et al,2016)

Epigenetic interactions lead to transcriptional regulation. These epigenetic events affect the initiation and progression of cancer that might deviate from the histone modification, promoter regions methylation, chromosome position, and remodeling of chromatin. (Debina et al, 2015

The variability of epigenetic helps the makeup of phenotypic individually (such as DNA repair capacity, xenobiotic metabolism, immunity) but it has a risk to get malignancy where some metabolites can disturb the activity of epigenetic modifiers. (Scott et al, 2016)

One of the mechanisms of cancer metabolism is where there is an oncometabolite that the accumulation will regulate the activity of the epigenetic enzyme. (Kim, 2017)

The levels of genetic and epigenetic can impact the activation of regulatory proteins and the signal transduction pathways. The DNMT normally add the methyl groups to the hemimethylated CpG sites for maintaining the pattern of methylation for the next generation which is done by methylases. (Jones, 2019)

The DNMTs family helps the CpG methylation de novo pathway where it works in the maintenance of methylation during replication. (Chen et al, 2006) It starts from the DNMT1 leads the methylated models of CpG regions is multiplied on the current DNA synthesis. (Ghavifekr et al, 2013) Thus, DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B) has been targeted in epigenetic therapy. This therapy will be discussed in the part of therapeutics. (Wongtrakoongate et al, 2015)

As it is seen in Figure 6 (part of the stochastic model), the methylated CpG sites and a silenced tumour suppressor gene are seen that enhance the growth of the cells. This maintenance of this progress is done by the methylase. (Kazanets, 2016) In the part of the instructive model, it is seen that the yellow circle which is an activated oncoprotein guides the tumour suppressor gene through the pattern of a classical transcriptional that involve the SS-DBP or sequence-specific DNA binding protein, also the green circle that shows the corepressor complex and DNA methylase. When there is any loss from these components, there will be a loss of DNA methylation and affect the tumour suppressor gene expression. (Zhang, 2012) (Lopez-sera et al, 2008)

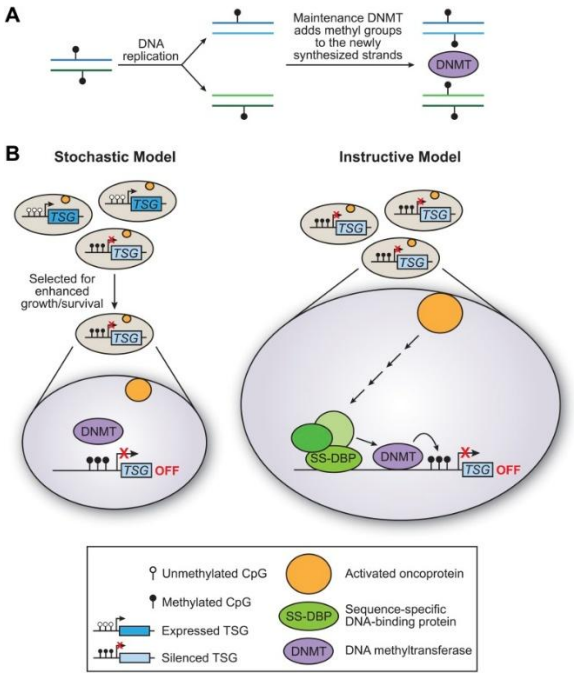

Figure 6. The stochastic and instructive models for DNA methylation of tumour suppressor genes. (Struhl, 2014)

Source: Struhl (2014).

Roles and Examples of Genes Affected By Epigenome Modifications in Lung Cancer (Due To Smoking)

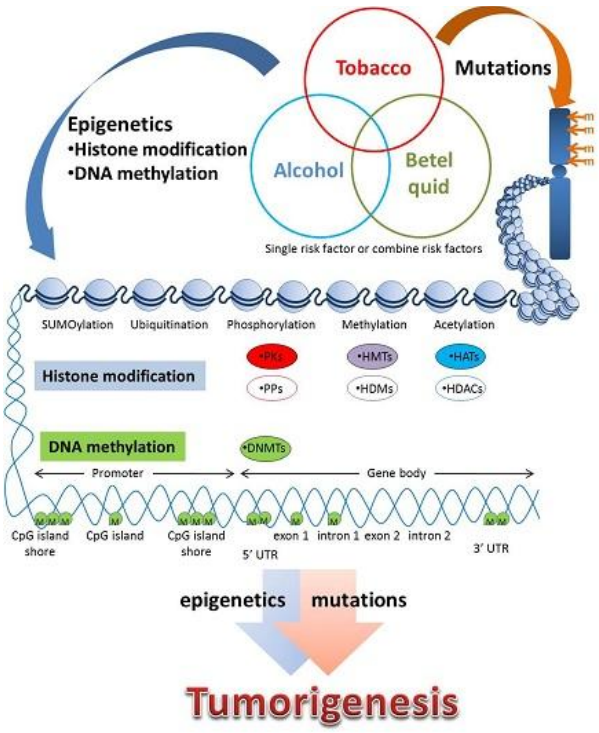

Figure 2. The progress of a few factors from environment that affect the epigenetic and leads to cancer. (Tong-hong *et al.*2017*)*

Source: Tong-Hong et al. (2017).

Recently, it was found that the environmental factors can lead adaptive has some response in the cell and some changing in the modification of epigenetics. (Suarez *et al*, 2015) The study of the epigenetic changes that are caused by environmental toxins is called toxico-epigenomics. Many scientists have found that epigenetic modification of genome has a relationship with the exposure to chemicals that leads to cancer. (Verma, 2018)(Reamon *et al*, 2008) The environmental pollutant that is present in the air has been discovered that these chemicals can modify the DNA or histones and affect the enzyme activities through either inhibition or stimulation in the epigenetic control. (Nivedita *et al*, 2018) However, in this topic, we want to focus more on cigarettes.

As cigarette smoke can induce the DNA changes, it also induces the epigenetic changes that cause some changing in a few mechanisms such as receptors, signaling pathways, cell cycle regulators, angiogenic factors, invasive, apoptosis, and metastasis mediators. (Chen *et al*, 2011) DNA methylation can control the gene expression for the level of protein production without changes the structure of DNA, but the quantitative trait depends on the genetic and environmental factors. (Ken *et al*, 2013)

NNK (Nicotine-derived nitrosamine ketone)

One of the environmental factors which are the most effective pulmonary carcinogen from tobacco is a chemical NNK (Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone). (Peterson, 2017) The nitrosation of the nicotine produce NNK that is known as the most powerful carcinogen from cigarette smoke. (Jin *et al,* 2004) The formation of NNK could be detected clearly by mass spectrometry and by high-performance liquid chromatography.

NNK can induce the lung carcinogenesis but it depends on the administration route. The concentration in every cigarette is also different. Mostly is 20-310 ng/cigarette. (Hecht, 2014)

In the body, the enzymes break the NNK and help them to damage the DNA. This changing normally is seen in lung cancer cell where it starts from the DNMT1 which is induced by NNK. (Hetch *et al*, 2002) NNK does not change the mRNA but prolongs the DNMT1 stability through AKT signaling that inhibits the GSK3β/β-transducin repeat that contains the protein and mediates the degradation of the protein. It causes an accumulation of DNMT1 protein and hypermethylation. (Lin *et al,* 2010) (Seveerin *et al,* 2011) The catalyzation of NNK cytochrome has two main pathways such as αmethylhydroxylation or αmethylenehydroxylation. Both can produce carcinogenic intermediates. (Akopyan, 2006)

If the DNA is not repaired as fast as possible, it will cause gene mutation permanently and causes cell proliferation and transformation uncontrollable. (Tian-Rui *et al*, 2015)

As a matter of fact, hyper- and hypo-methylation can cause tumor suppressor genes to be silenced. (Costelloa *et al*, 2001) Normally, this overexpression leads to abnormal *de novo* promoter-CpG islands and cause the transformation of malignant. (Hsieh *et al*,2010)

Carbon Monoxide

After being inhaled, carbon monoxide binds to the haemoglobin to create carboxyhemoglobin (COHb) in erythrocytes and being transported to the bloodstream. When it occurs, there is no oxygen that is not able to bind on the same cell even though to the different receptor. Furthermore, CO acts faster than oxygen and exit from the haemoglobin slower than oxygen. Thus, CO always gets the haemoglobin before the oxygen can do it and causes starvation of oxygen in human body (hypoxia). (Blumenthal, 2001)

Hypoxia which is also called as oxygen deprivation. It is a characteristic of tumours that causes instability of the genomic. Therefore, hypoxia becomes a therapeutic target in cancer. However, the result of this therapy is very poor. (McKeown, 2014) Because of that, the hospital prefers to use DNMT inhibitor treatment rather than Hypoxia treatment.

As hypoxia is a phenomenon that is common in a malignant tumour progression. It is started where the hypoxia rises the number ROS (Reactive Oxygen Species) production and assists the tumour cell survival and progression. (Muz, 2015) ROS induces the hypermethylation through the up-regulation of the DNMT expression. This pattern is implicated with malignant transformation and the tumour progression.

Therapeutics

As the cigarette affects the DNMT's family, the most commonly used is the DNMTs inhibitors those are nucleoside analogs 5-azaC, 5-azaCdR, and Zebularine. Each of them has their own unique way. The nucleoside analogs are fused into DNA in the middle of DNA synthesis progress. DNMT1 creates the covalent bond at the 6 positions of cytosine with the carbon together with 5-aza cytosine ring. (Flotho, 2009)

In the normal condition, the group of methyl is transferred to cytosine ring at the fifth position of the carbon from SAM. It helps the enzyme is released to cytosine from the covalent bond. Then, the 5'-aza-cytosine rings switch the cytosine to causes the methyl displacement could not take place and DNMT is trapped in. (Svedruzic *et al*, 2005).

The progress of replication without DNMT1 will be seen in the new strand where there is a passive loss of DNA methylation. Another than 5-azaC, there is zebularine which is chemically unstable and can do orally. (Subramaniam, 2014)

CONCLUSION

This narrative literature review concluded that smoking exposure contributed significantly to lung cancer development through complex toxico-epigenomic mechanisms involving chemical carcinogens and epigenetic dysregulation. Tobacco-derived compounds, particularly nicotine-derived nitrosamine ketone (NNK) and carbon monoxide, played important roles in disrupting normal cellular regulation. NNK promoted carcinogenesis by increasing DNA methyltransferase 1 (DNMT1) stability, inducing aberrant DNA methylation patterns, and contributing to the silencing of tumor suppressor genes, whereas carbon monoxide promoted hypoxic conditions and reactive oxygen species (ROS) generation that further enhanced epigenetic instability. These molecular alterations affected essential biological processes, including cell proliferation, apoptosis regulation, DNA repair, and tumor progression. Therefore, understanding the interaction between tobacco toxicants and epigenetic mechanisms provides valuable insights into the identification of potential biomarkers and the development of targeted therapeutic strategies, including DNA methyltransferase inhibitors.

Future research should further investigate specific epigenetic biomarkers associated with smoking-induced lung cancer through experimental and clinical studies involving larger and more diverse populations. Additional studies should explore the therapeutic effectiveness, safety, and molecular mechanisms of epigenetic-targeted treatments, such as DNMT inhibitors, across different lung cancer subtypes. The integration of multi-omics approaches, including genomic, transcriptomic, and epigenomic analyses, may provide a more comprehensive understanding of how tobacco exposure initiates and accelerates malignant transformation.

Such investigations are expected to support the development of earlier diagnostic approaches and more personalized therapeutic strategies for patients with smoking-related lung cancer.

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CONFLICT OF INTEREST

The author states that there are no conflicts of interest, whether personal, commercial, or financial, that can affect the implementation and results of this study.

AUTHOR'S CONTRIBUTION

Hana Sarvella contributes to research design, data collection and processing, system development, result analysis, and article manuscript preparation.

GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

In the process of compiling this article, the author uses generative artificial intelligence (AI) as a tool in language refinement, writing structure, and grammar improvement. The use of AI is carried out on a limited basis and remains under the supervision of the author. All data, analysis, interpretation, and scientific substance in this article have been checked and verified by the author. The author is solely responsible for the accuracy, authenticity, and final content of the manuscript.

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