International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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Epigenetic Mechanisms and Development of Disorders

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International Journal of Science and Research Archive, 2025, 17(02), 558-566

Publication history: Received on 05 October 2025; revised on 11 November 2025; accepted on 14 November 2025

Article DOI: https://doi.org/10.30574/ijsra.2025.17.2.3054

Abstract

Epigenetic disorders play a crucial role in modern medicine. As traditional disorders are becoming increasingly treatable the margin between cancers and bacterial infections is increasing. Epigenetics is a relatively new focus in medicine lacking complete understanding; therefore, it is imperative to improve knowledge in epigenetic mechanisms responsible for molecular alterations within cells. Key epigenetic processes regulate gene expression without altering the underlying DNA sequence, thereby leading to aberrant changes in cells that promote development of epigenetic disorders. These findings highlight the dynamic nature of epigenetic modifications as both contributors and potential therapeutic targets in disease pathogenesis. Understanding these mechanisms provides opportunities for improved diagnostics, personalized treatment and preventive strategies in complex disorders influenced by genetic and environmental interactions.

Keywords: Epigenetics; Epigenetic Disorders; DNA Methylation; *Helicobacter Pylori*; Schizophrenia; Lung Cancer; Gastric Cancer

1. Introduction

For a long time, modern medicine had a lack of consensus on the underlying causes and molecular interactions of complex disorders, such as cancers. Often, prevailing explanations such as traditional Mendelian genetics were insufficient to elaborate on the full diversity of complex disorder origins. With the advent of novel sophisticated technology, studying such complex disorders has become more accessible than ever. This led to uncovering the emerging field of epigenetics and understanding of complex polygenic and epigenetic disorders.

Understanding the molecular mechanisms involved in pathogenesis of such disorders has become a crucial goal in medicine of the 21st century in order to advance in diagnostics, treatment and prevention of some of the most fatal and distressing disorders. This article aims to shed light onto a spectrum of current health concerns tied with epigenetic roots.

2. Epigenetic mechanisms

There are three distinct epigenetic markers of interest when studying the epigenetics of various disorders. Namely, DNA methylation, histone modifications and non-coding miRNAs have been identified to all play a role in the pathogenesis of many cancers, neuropsychiatric disorders as well as others [1]. Epigenetic mechanisms, such as DNA methylation and histone modifications affect the structure of the DNA-protein complex, chromatin, thereby affecting transcription.

Epigenetic modifications can alter the degree to which chromatin is wound up. Euchromatin, chromatin which is less tightly wound, has much easier access to transcription and allows the gene to be transcribed. On contrary,

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heterochromatin is wound up much more tightly and blocks the transcription factors from accessing a promoter region of a particular gene.

2.1. DNA Methylation

Alterations in DNA methylation have been detected in many various disorders featured in this article. The process of DNA methylation is catalyzed by DNA-methyltransferases (DNMTs), which transfer methyl groups to DNA, in particular attaching the methyl group onto a cytosine in a CpG sequence, resulting in 5-methylcytosine as shown on Figure 1 [1,2,3]. The methylation of CpG islands (clusters of CpG sequences) in promoter regions of genes usually represses the transcription by wounding chromatin more tightly around histones as shown in Figure 2 and functionally inactivates the gene from being translated into a protein product or deactivating regulatory function.

The reverse is also possible, as TET enzymes can catalyze the 5-methylcytosine to 5-hydoxymethylcytosine. The resultant DNA demethylation reactivates the gene for transcription. The methylation of DNA is a highly dynamic process, allowing a range of phenotypes and expression of genes [3]. DNA methylation is one of the most occurring and well-studied epigenetic alterations in genes involved in cell regulatory functions, including proliferation, cell cycle regulation, DNA repair, apoptosis, cellular adhesions and motility [4].

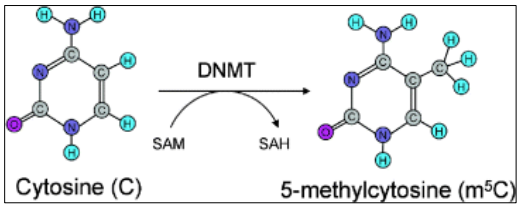

Figure 1 Methylation of cytosine. Cytosine residues in DNA are converted to 5-methylcytosine by DNA methyltransferases (DNMTs). The methyl group is donated by the universal methyl donor S-adenosylmethionine (SAM), which is converted to S-adenosylhomocysteine (SAH) [11]

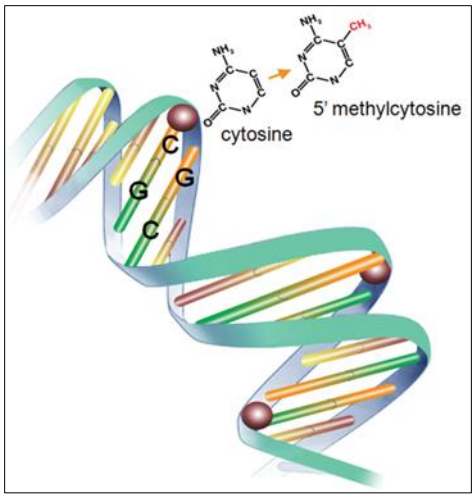

Figure 2 Methylation of DNA occurs at cytosine residues when present as CG dinucleotides. Methylation occurs by the addition of a methyl group at the 5' site of cytosine (depicted as shaded sphere) [7]

2.2. Histone Modification

Histones are proteins onto which DNA coils around in nucleosome complexes. In eukaryotic cells, DNA is wrapped into chromatin in the nuclei. A nucleosome is comprised of 146-147 base pairs of DNAS and a histone octamer with one H2A-H2B tetramer and two H3-H4 dimers. Histone modifications are known as histone methylation, histone acetylation and histone phosphorylation. Histone methylation, which usually occurs on the lysine residues of histone H3 and H4 by adding methyl groups, is one of the most important post-transcriptional modifications.

Methylation of histones is catalyzed by Histone methyltransferases (HMT), which uses S-adenosylmethionine (SAM) as the substrate to transfer methyl groups onto lysine residues of histones. These can be methylated in varying degrees, resulting in active or repressive marks of gene expression. Histone acetylation is carried out by histone acetyltransferases (HATs) [3,5].

2.3. Non-coding miRNA

Non-coding miRNA (miRNA) are small RNA molecules involved in repressive regulation of gene expression. This is accomplished when miRNAs bind to mRNA and inhibit translation by degrading the mRNA molecule, effectively preventing translation. Initially, miRNAs are transcribed as primary transcripts (pri-miRNAs) and processed by Drosha and Dicer enzymes into mature miRNAs. Mature mRNA is incorporated into the RNA-silencing complex, which targets mRNA through base-pairing on the 3' untranslated region.

3. Epigenetic disorders

Epigenetic disorders arise from abnormal regulation of gene expression without changes in the DNA sequence. These abnormalities occur through aforementioned epigenetic mechanisms that disrupt normal gene expression, by silencing or activation, thus leading to aberrant expression of crucial oncogenes or suppression of tumor suppressor genes.

DNA methylation alterations are among the most studied causes, frequently involving hypermethylation of promoter regions that silences gene expression. Meanwhile global hypomethylation of the genome leads to genomic instability.

A wide spectrum of disorders are caused by epigenetic alterations, notably including lung and gastric cancer, neuropsychiatric disorders, cardiovascular disorders, as well as Type II Diabetes [6,7].

3.1. Gastric Cancer

3.1.1. Overview

Gastric cancer remains to be a global health concern, demanding great care for treatment from researchers and healthcare workers. Recent studies estimate a million new gastric cancer cases annually [8]. However another major issue is the relatively high morbidity rate, which is second only to lung cancer, making it one of the most fatal malignancies, especially in underdeveloped countries which lack sophisticated screening technologies, thus resulting in diagnoses of late-stage tumors. The high mortality rate is likely associated to the current methods of treatment, which are largely inefficient at curing cancer and in most cases only palliative, as gastric cancer is resistant to treatment by surgery, chemotherapy and radiotherapy. Thus, advanced stages of gastric cancer have poor prognosis [8].

As medical technology and lab analysis techniques improve, an immense amount of new information for research is available. Recent studies have yielded a new field of interest when studying cancer epigenetics. Elucidation for the underlying molecular basis of cancers, such as gastric cancer, has become increasingly studied. Gastric carcinogenesis is mostly explained by infection of the bacterium *Helicobacter Pylori* (*H. pylori*). The bacterium has already been defined as a definite carcinogen by the World Health Organization in 1994, and its effects largely explained by numerous studies [9]. Depending on the study, the degree of the effect of *H. pylori* varies, however some studies have found that up to 98% of patients' gastric cancer could be attributed to the presence of *H. pylori.* The relevance of *H. pylori* goes beyond the incidence rate in gastric cancer patients, as over 50% of the human population has been affected by *H. pylori*. Despite the high incidence rate, only 5% of *H. pylori* patients developed gastric cancer within ten years [6,8,9]. Up until quite recently, most of cancer predisposition in gastric mucosae was explained by the presence of cells with genetic alterations, however the effect of epigenetic alterations in recent studies often prevails the traditional sense of purely genetic component [10]. This increasingly indicates the significance of understanding the molecular behaviors of the interaction of *H. pylori* and the epigenome in order to develop treatments against gastric cancer.

The onset of gastric carcinogenesis can be largely explained by genetic and epigenetic alterations in cells of tissues in gastric mucosae and epithelial cells [10]. A major player in oncogenesis is DNA methylation, which functionally disables function of key genes. It is notable that these alterations take place in oncogenes, tumor-suppressor genes and tumor-related genes, which include genes involved in cell-cycle regulation, cell adhesion, and DNA repair and telomerase activation [8]. The onset of tumorigenesis is likely caused by the promoter hypermethylation of the aforementioned genes, resulting in transcriptional gene silencing and consequently loss of protein product [6]. Studies have found the relevant genes associated with gastric cancer: CDH1 (E-cadherin), APC, hMLH1, COX-2, p16 and RUNX3. Many other genes have also been explored, such as MGMT, p14, DAPK, GSTP1, RASSF1A, THBS1, TIMP-3, CHFR, DCC, PTEN, TSLC1, MAGE and SNCG [8,10].

It was observed that in non-neoplastic cells of gastric cancer patients, those which are adjacent to the neoplasm, there is an increase in promoter hypermethylation of the above-mentioned genes, in particular CDH1. The earliest epigenetic alteration in gastric carcinogenesis likely occurs in CDH1 methylation. CDH1 inactivation has been associated as the main molecular event in dysfunction of cell-cell adhesion, thus triggering tumorigenesis and promoting metastasis.

Extensive research into the histological and physiological behaviors between *H. pylori* and gastric mucosal epithelial cells have yielded greater consensus of the mechanisms responsible for the onset of gastric carcinogenesis. Most alterations caused by have been identified to have a bacterial component and host component.

3.1.2. Bacterial Component

Numerous studies have determined *H. pylori*'s spectrum of influence on gastric mucosal cells. Gastric inflammation by *H. pylori* likely triggers the epigenetic mechanisms responsible and the carcinogenesis cascade. A distinct characteristic of cancerous cells is overall genome-hypomethylation and regional hypermethylation of CpG islands, particularly in the promoter region of most genes. Widely studied epigenetic mechanisms such as DNA methylation have been observed to inactivate genes such as hMLH1 or RUNX3, namely by hypermethylation in the promoter region, rather than exons, as exon methylation still often results in somewhat useful transcript products that retain partial useful function [10]. Genome-hypomethylation results in activation of typically heavily methylated genes, resulting in synthesis of aberrant protein products, thus the presence of *H. pylori* increases the genetic instability in the tissue. Silencing of hMLH1 has been associated with microsatellite instability (MSI) in the tissue [8]. MSI indicates the presence of cells with replication errors in simple repetitive microsatellite sequences, due to lack of the mismatch repair, often when genes such as hMLH1 are silenced [8]. The interest in MSI is due to its frequent presence in malignant gastric tissue, suggesting a close association to gastric carcinogenesis [8]. Table 1 demonstrates the effect of various carcinogenic factors comparing *H. pylori* positive and negative patients in a clinical study.

Table 1 Clinical Features of Patients Sorted by the Presence of *H. pylori* (Hp) Infection and Intestinal Metaplasia (IM) [6]

Clinical Feature	**Group A *Hp*− (IM−) (N = 12)**	**Group B *Hp*+ (IM−) (N = 28)**	**Group C *Hp*+ (IM+) (N = 17)**	***P***
Mean age (yr ± SD)	45 ± 13	51 ± 11	57± 14	A *vs* B: 0.18∗ A *vs* C: 0.03∗ B *vs* C: 0.17∗
Male (%)	4 (33%)	10 (36%)	8 (47%)	A *vs* B: 0.88ǂ A *vs* C: 0.46ǂ B *vs* C: 0.45ǂ
Smoking (%)	4 (33%)	4 (14%)	4 (24%)	A *vs* B: 0.17† A *vs* C: 0.43† B *vs* C: 0.34†
Alcohol (%) (>40/60 g/d)	2 (17%)	7 (25%)	7 (41%)	A *vs* B: 0.44† A *vs* C: 0.16† B *vs* C: 0.25†
Red meat (%) (≥200 g × 3/wk)	9 (75%)	21 (75%)	15 (88%)	A *vs* B: 0.66† A *vs* C: 0.33† B *vs* C: 0.28†
Vegetables (%) (≥200 g × 5/wk)	11 (92%)	26 (93%)	17 (100%)	A *vs* B: 0.67† A *vs* C: 0.41† B *vs* C: 0.38†
Family history of gastric cancer (%)	2 (17%)	4 (14%)	2 (12%)	A *vs* B: 0.62† A *vs* C: 0.51† B *vs* C: 0.53†

∗Student's *t*-test.
†Fisher's exact test.
ǂPearson's $\chi 2$ test.

It is worth mentioning that although epigenetic silencing of tumor suppressor genes, namely RUNX3, hMLH1, CDKN2A, CDH1, p16 and p53, plays a crucial role in the onset of the malignancy by inhibition of DNA repair and apoptosis, it is not limited to genes with such function [10]. Genes such as EGF-like and insulin-like growth factor genes, with no apparent cancer inhibiting function are very frequently observed to be inactivated in gastric tissue, thus stimulating carcinogenesis [8,10].

Additionally, many studies on gastric mucosae of *H. pylori*-positive and *H. pylori*-negative patients have outlined a few key differences in the tissue. In general, a tendency for overexpression of Cyclooxygenase-2 (COX2), nitric oxide and their respective products have been observed in malignant lesions, which largely return to normal levels, excluding COX2 in some cases, after *H. pylori* eradication [8].

3.2. Host Component

Genetic predisposition affecting risk and severity of inflammation, as well as acidity is often linked to enhance the effects of *H. pylori*. The most widely reported genes are LL1B and NAT1. However, the effect of these polymorphisms behaves in a spectrum and is thus difficult to explain the association of the mentioned genes with *H. pylori* [8].

Genetic predisposition independent of acidy has also been reported. Hereditary predisposition may also play a role in the onset of carcinogenesis. Recent studies on hereditary non-polyposis colorectal cancer patients, who subsequently developed gastric cancer, were frequently observed to have faulty DNA mismatch repair genes such as hMSH2 or hMLH1, thus increasing MSI levels. Thus, the hereditary component can increase the risk and onset of gastric carcinogenesis on top of *H. pylori* infection [8].

As of now, there is lack of confident consensus of mechanisms induced by the host, independent of *H. pylori* that stimulate gastric carcinogenesis, indicating an imperative for more research in this field, to achieve a global picture of the disorder [8].

3.3. Schizophrenia

3.3.1. Overview

Schizophrenia is one of many complex psychotic disorders that affect the central nervous system, impairing function of the prefrontal cortex. This leads to many symptoms, such as hallucinations, lack of social ability and disorganized thoughts [1,12]. Studies have found that up to 1% of the world population can be described as having symptoms of schizophrenia [1]. This results in high economic costs and distress in our society, suggesting an imperative to understand and prevent schizophrenia. Unfortunately, as with many complex brain disorders, a large part of the causes remains unexplained and require further study [1,12].

Although schizophrenia has high heritability, most causes rely on epigenetic interactions, in particular DNA methylation. A large part of schizophrenia development remains unexplained due to the complex polygenic and epigenetic processes involved in its development [1,12]. Even in the case of monozygotic twins, the risk of developing schizophrenia is only 50%, indicating a crucial association of epigenetic influences in the development [1,12]. A crucial factor was noted to be the influence of the environment during critical and vulnerable stages of development of the central nervous system [12]. In schizophrenia, the spectrum of influence ranges from molecular mechanisms to social environments and traumatic experiences, leaving the root cause largely undetermined, but likely a product of many circumstances. There are many epigenetic mechanisms contributing to the development of this disorder. This section aims to provide insight into current explanations available for the epigenetic basis of schizophrenia [3].

DNA methylation has been detected in schizophrenia by the increased activity of DNMTs in the brains of schizophrenia patients, causing hypermethylation of promoter regions, thereby causing downregulation of schizophrenia-associated genes such as GAD1, BDNF, RELN and NR3C1 [3].

Histone 3 (H3) is particularly downregulated in schizophrenia, mostly by di- and tri-methylation of H3K9 and H3R27 which regulate GAD1 expression. This downregulation mostly occurs in cortical neurons and adjacent non-neuronal cells in post-mortem tissue from schizophrenic patients, thus reducing expression of genes typically associated with neuronal metabolism [3].

Several specific miRNAs have been associated with schizophrenia and other psychiatric disorders, in particular miR-132, miR-137 and miR-181b. The influence of miR-132 is particularly interesting as it is developmentally regulated during adolescence by N-methyl-D-aspartate signaling, and targets both MECP2 and DNMT3A [3].

3.3.2. Molecular Basis

Though specific genes are found to be inactivated in schizophrenia more than others, the candidate gene approach is largely ineffective in schizophrenia as it is difficult to pinpoint exact genes responsible. However, a recent study suggests that most genes affected are involved in the dopamine pathway and indicate an association of the dopamine pathway to the development of schizophrenia [3]. The candidate gene approach likely may not yield a particular gene, as schizophrenia is polygenic and epigenetic, while genes involved in its development may be on entirely different loci or chromosomes [12]. This suggests that most cases are likely derived from a complex set of factors, rather than a pure genetic component. As such, purely genetic alterations on coding or non-coding regions of a gene are unlikely to have direct stimulus on schizophrenia development [12].

In a molecular perspective, convincing observations have shown the significance in oxygen depletion during gravidity such as by smoking [12]. This has been closely associated with schizophrenia development, as neurodevelopment is extremely vulnerable during this period and right before birth, as many processes are switched on and off [12].

The apparent explanation for schizophrenic symptoms is likely associated with aberrant expression of the dopamine pathway, which has strong functional association, however lacks statistically significant loci to determine specific genes. Current candidate genes include DISC1, NRG1 and clusters of GABA-A receptor subunits on chromosome 5 [3].

The primary positive symptom of schizophrenia that can be measured is the upregulation of dopamine signaling in the brain [3]. Most effective antipsychotics against schizophrenia are targeting dopamine D2 receptors and most schizophrenia patients show high sensitivity to dopamine agonists [3]. This supports the involvement of the dopamine pathway in schizophrenia [3]. DNA methylation patterns are significantly different in neuropsychiatric disorders, resulting in a spectrum of clinical phenotypes and difficulty in diagnosis and coaggregation with other disorders, such as bipolar disorder [3].

In addition, an important role plays the major histocompatibility complex (MHC) on chromosome 6 [12]. Errors in the MHC are not unique to schizophrenia as Alzheimer's and Crohn's disease have been found to share MHC dysfunction [12]. This shows the complexity of the origin of schizophrenia.

3.4. Lung Cancer

3.4.1. Overview

Lung Cancer presents itself as a major global health concern due to its abundance, high mortality rate and lack of definitive treatment. In particular most recent research focuses on non-small cell lung cancer (NSCLC), as it accounts for the vast majority of lung cancers studied (80%) [13]. An increasingly relevant sub-topic is lung squamous cell carcinomas (LUSC), as they take up a large portion of NSCLCs [13]. Especially in the field of epigenetics, LUSCs are relevant due to their high association with environmental factors such as smoking, alcohol and infections. Smoking in particular have long been elucidated as a potent carcinogenic factor for various diseases including lung cancer of the LUSC subtype [13]. At the same time small cell lung cancer (SCLC) presents itself to be a significant health concern due to difficult diagnosis and bleak prognosis.

3.4.2. Non-Small Cell Lung Cancer

The epigenetic landscape for studying LUSCs has been rapidly progressing for the last decade with greater insight into molecular mechanisms responsible for changes in cellular machinery leading to oncogenesis. A significant player in lung cancer development seems to be CDKN2A producing the tumor suppressors p16 and $p14^{ARF}$, both encoded in the INK4a locus on chromosome 9p21, often heavily methylated in the promoter region in LUSCs, leading to its inactivation [14]. Under normal conditions p16 inhibits cyclin-dependent kinase 4 in malignant cells during the G phase of the cell cycle, however following its suppression tumorigenesis accelerates in absence of the inhibitor. Higher expression of p16 positively correlates with longer patient survival time. The intertwined cooperation between p16, p53 and RAS genes effectively abrogate growth control by induction of apoptotic cell death [14].

Smoking has been elucidated to be one of the most significant factors linked to development of lung cancer. As aforementioned, p16 is a key tumor suppressor gene involved in maintaining genomic stability and integrity. Data in Figure 3 suggests have found that squamous cells are most susceptible to p16 methylation. Study results have identified current smokers to be much more likely to have methylated p16 than non-smokers. Methylation of p16 positively correlates with pack-years smoked as shown on Figure 4, duration of smoking and negatively associated with time since quitting smoking. This relationship illustrates the impact and correlation between smoking and lung cancer.

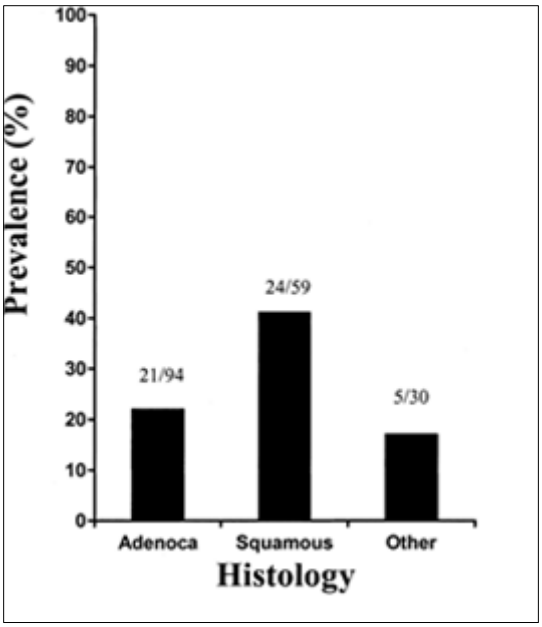

Figure 3 Frequency of methylation of p16 promoter region by histology in NSCLC. Columns, proportion of methylation of the p16 promoter region in each histology [14]

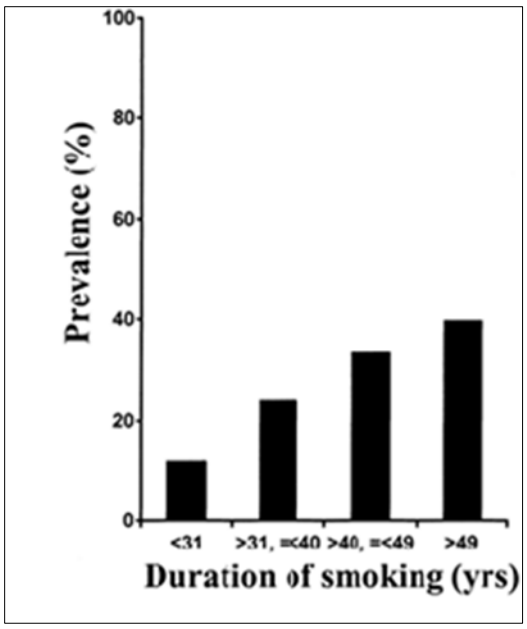

Figure 4 Frequency of p16 methylation by quartile, according to duration of smoking in all of the NSCLC patients studied. The association between methylation of p16 promoter region and duration of smoking was calculated by Wilcoxon rank sum test. The unit of duration of smoking is years. Columns, proportion of methylation of p16 promoter region in each quartile of smoking [14]

3.4.3. Small Cell Lung Cancer

Small cell lung cancer (SCLC) is also a potent lung cancer subtype due to its highly metastatic and neuroendocrine nature, resulting in a high mortality rate. SCLCs constitute approximately only 13-15% of lung cancer cases; however have bleak prognosis and life expectancy. Treatment therapies are largely ineffective due to the metastatic nature, recalcitrant behavior and late diagnosis.

Interestingly, SCLCs are accompanied by high mutational rates and genomic instability. The likely cause of this may be related to frequent loss of function mutations in TP53 and retinoblastoma 1 (RB1), which are the primary tumor suppressors which maintain genomic integrity. The continued accumulation of loss of function in tumor suppressors leads to different epigenetic alterations that ultimately result in aberrant regulation of key DNA repair/housekeeping genes, oncogenes and other tumor suppressor genes. The main cause of SCLC development is the inactivation of tumor suppressor genes by promoter hypermethylation. Alterations of other genes, such as inactivation of PTEN tumor suppressor, amplification of MYC family members, mutations in KMT2A (MLL), KMT2D (MLL2), EP300, CREBBP, histone-modifying proteins encoding genes, NOTCH family genes, FHIT and CDKN2A genes have been frequently documented in SCLCs indicating a likelihood for association with SCLC. It is noteworthy that inactivation of tumor suppressor genes such as TP53 are universal in most cancer types, while others are unique to SCLCs [4].

4. Conclusion

The study demonstrates that aberrant epigenetic mechanisms, including DNA methylation, histone modification and non-coding RNAs play a crucial role in the development of complex disorders caused by altering gene expression. These insights will aid in advancing diagnosis and treatment, with personalized medicine showing much promise in the coming years.

Compliance with ethical standards

Acknowledgments

I am grateful to Dr. Ivan Zalesov for his continued support in revisions of my article and Mr. Hector MacDonald for his support as my school principal.

Disclosure of conflict of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of this article.

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