EPIGENETIC MODIFICATION IN RELATION TO SOME COMMON CANCERS

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Abstract

Epigenetic modification is a process that regulates DNA sequences without altering the original structure of the DNA sequences. The distortion of DNA by epigenetic modification can turn gene expression off or on. Several scientific pieces of evidence have shown that the regular occurrence of a genetic mutation governed by epigenetic changes can subsequently usher in the onset of many diseases, including Cancer. DNA methylation and histone modifications, such as acetylation, methylation, and ubiquitination, which are well known to influence gene expression,

are among the most frequent epigenetic changes. In this review, we ostensibly review epigenetic modifications and their relation to cancer development. We observed that many epigenetic changes in gene expression are actively linked to Cancer, and it remains one of the most potential areas in cancer research. Many epigenetic mutations are repeatedly detected in cancer research, and reversing these mutations in cancer cells can lead to the discovery of novel therapeutic approaches and cancer biomarkers.

Keywords: Cancer, Epigenetics, DNA, genes.

1.0. Introduction

Epigenetics involves the changes that affect the expression of genes without changing the underlying mechanism of gene expression. It encompasses the mechanism and factors that affect how genes are expressed. However, these changes are reversibly dependent on the factors that influence the alteration of the expression of genes (Eleni & Paraminder, 2022).

Epigenetics reprogramming helps regulate some crucial processes in the cell, including cell growth, proliferation, and differentiation. Abnormalities in these critical processes can result in Cancer, autoimmune diseases, cardiovascular diseases, metabolic diseases, and myopathy (Eleni & Paraminder, 2022; Anna & Portela, 2012). These effects are heritable, but they can also be reversed. Thus, epigenetic modifications could broaden the scope of understanding the etiology and treatment of diseases which could be potential biomarkers for diagnosing diseases.

Epigenetic modifications like methylation of DNA, post-translational histone modifications, histone variants, and involvement of non-coding RNAs have played a significant role in gene expression and regulation in plants and animals. These epigenetic modifications have produced a broader spectrum in expressing phenotype by the selective turning on and turning off of genes. Organisms (plants and animals) show variability in phenotype in response to the environment they are exposed to. These phenotypic variations accrued by epigenetic modifications can be passed down to their subsequent offspring and thus expressed (Kushal *et al.,* 2021).

Epigenetic modifications are fundamental to regulating many cellular processes, including gene and microRNA expression, DNA-protein interactions, suppression of transposable element mobility, cellular differentiation, embryogenesis, X-chromosome inactivation, and genomic imprinting. It is also crucial for plant survival against biotic pathogens such as viruses, bacteria,

fungi, insects and abiotic stresses such as cold, heat, and salinity. Additionally, alteration in the regulation of DNA methylation and demethylation can disrupt the susceptibility of plants to various stresses (Nagymihály *et al.*, 2017; Satgé *et al.*, 2016).

The primary mechanisms of epigenetic modifications include DNA methylation, post-translational histone modifications, and non-coding RNAs.

DNA methylation: Methylation of DNA is the most common and widely studied mechanism of epigenetic modification. It involves the transfer of a methyl group to a nitrogenous base (usually cytosine). The methyl group is usually donated from the cofactor S-adenosyl-Methionine (SAM) (Moore *et al.*, 2013).

Post-translational Histone Modifications: This includes histone acetylation, methylation, phosphorylation, and ubiquitination (Kushal *et al.*, 2021).

Non-Coding RNA: Non-coding RNAs (ncRNAs) are RNAs that are not translated into proteins. They participate in the regulation of gene expression (Kushal *et al.*, 2021).

In this review, we ostensibly review epigenetic modifications and their relation to cancer development. We discuss the epigenetic changes that occur in gene expression and regulations and point out potential areas in cancer research.

2.0 Epigenetic Modifications, principles & types

2.1. *DNA Methylation*

DNA methylation is the major element of epigenetics that regulate gene expression through the displacement of chromosomal architecture (Sumei & Wanyin, 2018). It involves adding methyl groups in DNA sequences without altering the structure of the genome.

DNA methylation involves adding a methyl group (-CH3) at carbon five of a cytosine base of CpG dinucleotides. This DNA modification is an essential factor involved in transcriptional regulation, and its defect can serve as a signpost to various diseases, including cancer. Hypomethylation and hypermethylation are the only two methylation defects that exist in DNA methylation (McMahon *et al.*, 2017).

DNA hypermethylation is the addition of methyl group by DNA methyltransferases (DNMTs)—a family of enzymes that include DNMT3a, DNMT3b, and DNMT1. DNMT1 maintains DNA methylation sequencing already established by DNA replication. This methylation often occurs at the promoter CpG islands. However, hypermethylation results when DNMT3a and DNMT3b target unmethylated CpGs and initiate methylation (Kinney & Pradhan, 2012).

DNA hypomethylation is the absence of DNA methylation in genome regions, and it is a precursor to genomic instability and cancer tumor progression. In tumorigenesis, genome-wide hypomethylation is followed by a series of hypermethylation of localized promoter CpG islands, the same islands that are expected to remain unmethylation in healthy cells. This pattern is found in human tumor suppressor genes. It is noteworthy to mention that this pattern is specific to each individual and that it may lead to point mutation or deletions that allows tumor suppressor genes to be silenced (Nebbiolo *et al.,* 2018)

Mutation and deletion result in gene suppression; DNA methylation is also an alternative pathway to gene suppression. Methylation of the promoter region located at the 5'-end of the human genome, which is unmethylated, active, and allows expression, causes gene silencing. This methylation occurs in cytosine nucleotides, followed by a guanine nucleotide (CpG) (Goldberg *et al.,* 2007). Methylation of the CpG island is involved in, and plays a role in the regulation of transcription and changes during malignant transformation; thus, hypomethylation is commonly observed in malignant cells and is present in 70% of mammalian promoters (Baylin & Jones, 2011). DNA methylation reactions using SAM as the methyl donor are catalyzed by DNA methyltransferase (DNMT), resulting in 5-methylcytosine (Hervouet *et al.,* 2018).

DNMT1, 3a, and 3b have been identified in eukaryotes. DNMT1 is the most critical DNA methyltransferase enzyme in cancer development (Harb-De la Rosa *et al.,* 2015) and also recognizes DNA generated by hemi-methylated DNA replication. DNMT3a and 3b establish DNA methylation during embryo generation (Okano *et al.,* 1999). Mutations in methyl-binding proteins (MBD1, MBD2, MBD3, and MeCP2) and DNA methyltransferases are known to play a role in abnormal development (Robertson, 2005). Methylated E-cadherin promoter induces histone deacetylases (HDACs), which causes transcriptional silencing (Koizume *et al.,* 2002). Silencing of EZH2, which correlates with E-cadherin repression, has also been shown to inhibit invasive features of different cancer cells (Herranz *et al.,* 2008).

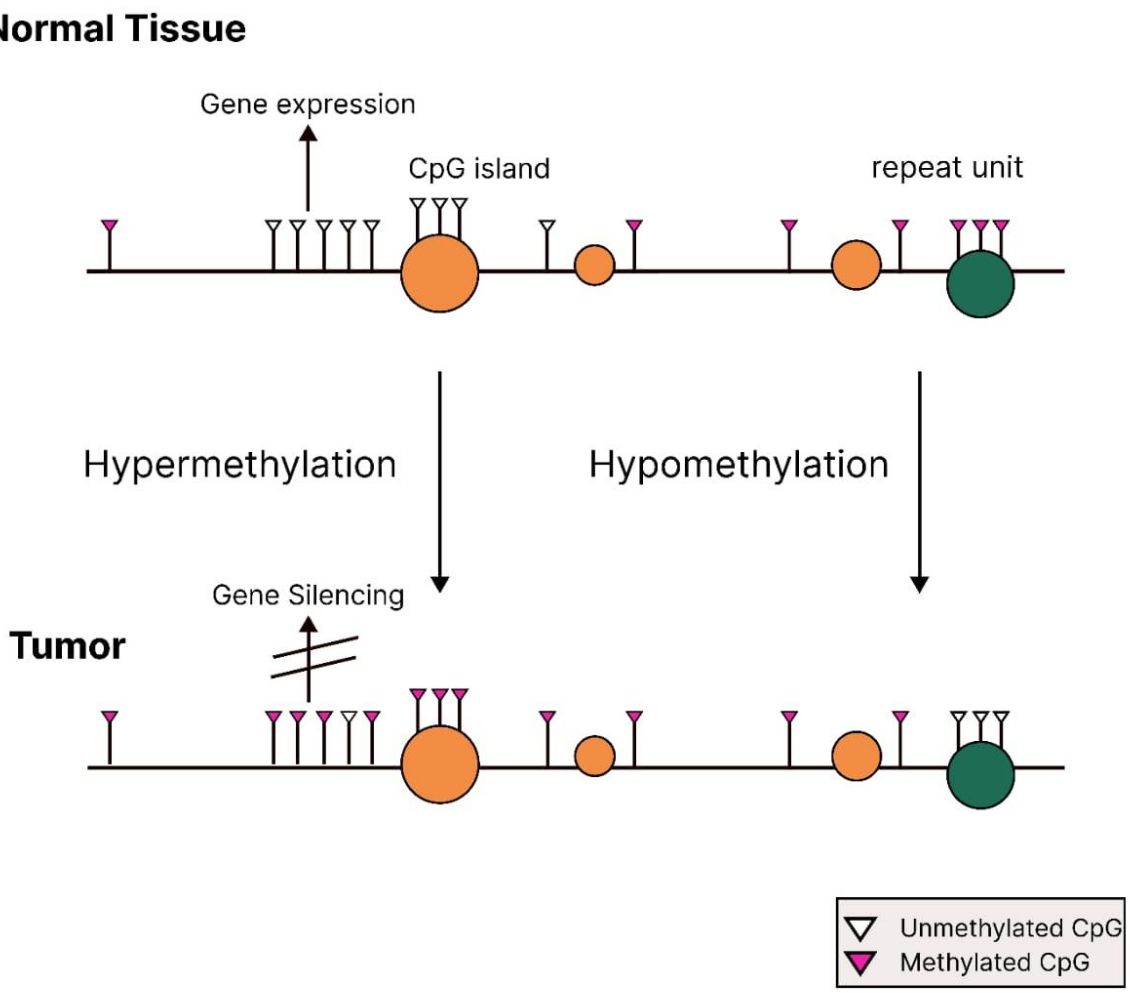

Fig 1: The regulation of gene expression in normal and malignant tissues by DNA methylation. In tumor cells, hypermethylation of DNA strands on the CPG island and/or hypomethylation of DNA strands on the repeat unit inhibit the function of the Tumor Suppressor Gene.

2.2. *Histone Modification*

This is a type of covalent modification that includes methylation, acetylation, ubiquitination, and phosphorylation. These post-translational modifications (PTMs) which occur on histones affect gene expression by altering chromatin structure or recruiting histone modifiers. Specific enzymes

catalyze these modifications at histone N-terminal tails, which have the amino acids lysine, arginine, serine, threonine, or tyrosine (Alaskhar *et al.,* 2018).

2.2.1. *Histone Acetylation*

This type of modification leads to an increase in gene expression (Kurdistani *et al.,* 2015; Gansen *et al.,* 2015). It is mediated by two groups of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). An acetyl group is usually transferred from Acetyl CoA to an amino acid (lysine) on the histone tails; this leads to the removal of the positive charges on the histones and thus reduces the relationship between histones and negatively charged phosphate groups on DNA. Overall, this makes chromatin less compact and more accessible to the transcription machinery. This process is repressed by HDACs, which catalyzes the removal of acetyl groups (Swygert *et al.*,2014).

2.2.2. *Histone Methylation*

This is catalyzed by histone methyltransferases (HMTs), which includes lysine methyltransferases (KMTs) and arginine methyltransferases (PRMTs), while histone demethylases (HDMs) mediate histone demethylation. The cofactor S-Adenosyl-L-Methionine (SAM) is usually the donor of the methyl groups to lysine or arginine residues of the histones catalyzed by HMTs. This modification indirectly influences the recruitment and binding of various regulatory proteins to chromatin. (Morera *et al.,* 2016; Kaniskan *et al.,* 2017)

2.2.3. *Histone Phosphorylation*

Two enzymes control histone phophorylation, the kinases and the phosphatases, which act by adding a phosphate group and removing the phosphate group from the histone, respectively (Sawicka *et al.,* 2012). Phosphorylated histones are involved in DNA damage repair, keeping chromatin structure during cell division (meiosis and mitosis), and regulating transcriptional activity (Rossetto *et al.,* 2012; Bannister & Konzarides, 2011). The phosphorylation of histones interacts with other histone modifications (Zippo *et al.,* 2009). For instance, phosphorylation of Histone H3 can affect the acetylation of two amino acids of the same histone (Alaskhar *et al.,* 2018).

2.2.4. *Histone Ubiquitination*

This modification is carried out by the enzyme histone ubiquitin ligases and ubiquitin-specific peptidases, which function in adding ubiquitin to the histone and removing ubiquitin from the histone, respectively (Schwertman *et al.*, 2016). Ubiquitin is a protein conjugated to substrate proteins by the ubiquitin proteasome system; histone ubiquitination functions in DNA damage signaling, regulation of transcription, and protein translocation. Polyubiquitination helps to identify a protein for degradation or its activation in some signaling pathways (Cao & Yan, 2012; Weake & Workman, 2008).

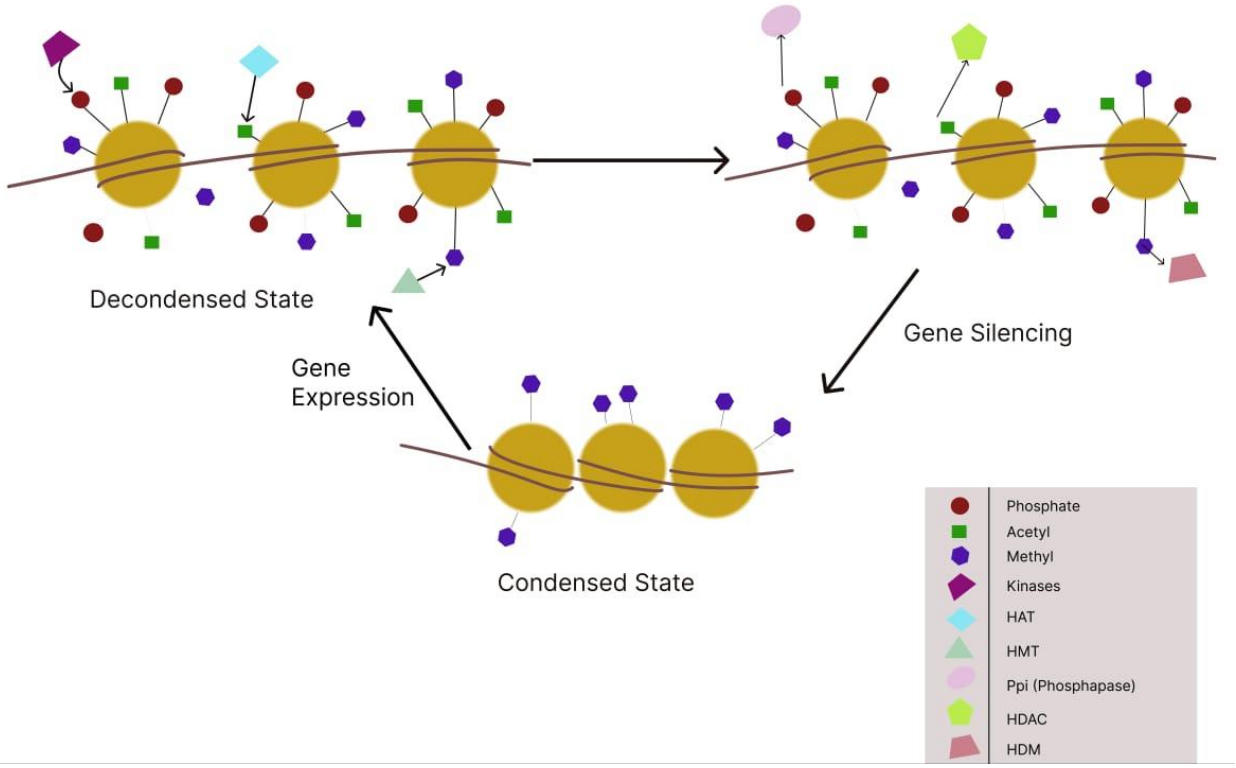

Fig 1: Histone Modification is depicted as alternating between condensed and decondensed states. The enzymes HAT, HMT, and Kinases catalyze the addition of acetyl, methyl, and phosphoryl groups to the histone in the decondensed form, respectively, making it less compact and hence accessible for transcription. This effect is inhibited by the enzymes HDAC, HDM, and phosphatase, which catalyze the removal of these groups and make the histone more compact (condensed).

2.3. *Nucleosome Remodeling and Non-Coding RNAs in Epigenomics*

The chromatin-containing eukaryotic genome is stored inside the nucleus, and it has developed as a method for dynamically regulating the genome and serving as a packaging mechanism. Chromatin is a complex of DNA and proteins that forms chromosomes within the nucleus. The remodeling of nucleosomes has made it possible to access the DNA despite the compact and protective chromatin organization. This makes it possible to regulate DNA access locally and differently as necessary. Nucleosome remodeling includes altering the connections between histone and DNA to disassemble, assemble, or move nucleosomes (Becker *et al.,* 2013; Klemm *et al.,* 2019; Karl *et al.,* 2022; Feng *et al.,* 2021).

Any RNA transcript produced from DNA that does not code for proteins is considered a non-coding RNA (ncRNA), i.e., any transcript outside of the exons within an mRNA transcript (Mattick & Makunin, 2006). Although the classification of ncRNAs is constantly changing as the field evolves, it is currently based on the length, functioning, and/or the genomic region from which the relevant transcript originates. Small non-coding RNAs are non-coding RNAs that are less than 200 nucleotides in length, while long non-coding RNAs are non-coding RNAs that are more than 200 nucleotides (Yan & Bu, 2021).

Recent research demonstrates that ncRNAs govern nucleosome remodelers' activity on various levels and that ncRNAs are their regulatory targets (Patty & Hainer, 2020). Interactions of chromatin remodelers with DNA methylation and histone variants have implicated their role in epigenomics (Klemm *et al.,* 2019). The epigenetic types of non-coding RNA modifications such as m6A, m5C, and m1A cause epigenetic consequences such as functioning as tumor promoters in cancer (Rong *et al.,* 2021).

3.0. Cancer and Epigenetics

Oncogenes and tumor suppressor genes (TSG) are widely known to be at the forefront of the onslaught of cancer. This is due to the frequent occurrence of mutation and epigenetic modifications. Cancer stem cells (CSCs) and stochastic or clonal evolution are also believed to be the promoters of cancer cells.

Cancer development remains problematic, but most studies show that environmental components and epigenetic alterations drive cancer progression. Cancer stem cells play a significant role in oncogenic transformation, while stochastic shows how oncogenes are obtained by none cancer stem cells (Yuanjun *et al.,* 2020). All the genetic information in cancer cells, including the mutations, is discernable. DNA methylation is one of the crucial elements in cancer advancement by slugging gene transcription and affecting the stability of chromatin. The fluctuation of DNA methylation influences a wide range of diseases, including cancer (Yuan *et al.,* 2019).

Targeting epigenetic modifications in cancer cells is one of the promising therapeutic strategies against cancer cells. The sophistication of epigenetic regulations require rigorous investigations of numerous thresholds in cancer therapy. The collective therapy targeting epigenetics exhibitions involving the inhibition of histone modification, DNA methylation, and inhibition of HDAC can effectively halt the manifestation of tumor-growth stimulating genes and simultaneously enhance tumor suppressor genes (Yuan *et al.,* 2019).

3.1. *The Earliest Indication of Epigenetic link to Cancer*

Gene expression and DNA methylation studies provide the earliest evidence of a connection between epigenetics and cancer. Numerous studies carried out in the past show that epigenetics is implicated in the development of cancer; some of the studies will be reviewed in this section.

In a research by Feinberg & Vogelstein, looking at variations between normal tissues and cancer cells, they found that CpGs (Cytosine-Guanine) sites that were methylated in normal tissues were unmethylated in cancer cells. Thus hypotheses have been put forward that DNA methylation might cause gene silencing in some tissues and ultimately lead to cancer in many groups (Feinberg &Vogelstein, 1983). In the process of oncogenesis, the inactivation of tumor suppressor genes is an important step. There is evidence that suggests that the development and regression of some retinoblastoma tumors may be caused by the changes in the methylation pattern of the retinoblastoma (RB) gene. This was done using methylation-sensitive restriction enzymes and a cloned DNA probe for the unmethylated CpG island at the 5” end of the RB gene (Greger *et al.,* 1989).

Alterations in DNA methylation is a crucial epigenetic step linked to cancer. Some carcinogens, for instance, cadmium, can act through this DNA methylation alteration. In a study conducted by

Takiguchi et al, they showed that cadmium effectively inhibits the activity of DNA methyltransferase and induces DNA hypomethylation after a week of exposure to this carcinogen (Takiguchi *et al.,* 2003). Esteller et al also suggested that cancer can be detected using DNA methylation markers. The study showed that gene promoter regions that are aberrantly methylated could give an insight into underlying tumor type evolution and improve cancer detection by providing molecular markers. They demonstrated that different tissues have different methylation profiles for CpGs associated with 12 selected genes [p16(INK4a), p15(INK4b), p14(ARF), p73, APC, BRCA1, hMLH1, GSTP1, MGMT, CDH1, TIMP3, and DAPK] (Esteller *et al.,* 2001).

Histone modification is another epigenetic mechanism that has a connection with cancer. Histone acetyltransferases (HATs) have been linked to leukemia and cancer (Yang, 2004). Lysine acetylTransferases (LATs) are crucial in genetic, molecular, and biological studies.

The loss of monoacylation and trimethylation is a distinctive feature of human tumor cells. Using immunodetection, capillary electrophoresis, and mass spectrometry, histone H4 post-translational modification was characterized in cancer cell lines, primary tumors, and normal tissue. This led to the discovery that there is a loss of a tri-methylated and acetylated form of H4 in cancer cells. These losses occurred at acetylated Lys 16 and trimethylated Lys 20 residues of Histone H4 (Fraga *et al.,* 2005). Loss of acetylation has also been established to be linked to cancer.

These earlier studies showed a connection between epigenetics and cancer, and newer studies have strengthened and corroborated these earlier claims (Ponomaryova *et al.,* 2020; Guo *et al.,* 2020; Wang *et al.,* 2020).

3.2. *Epigenetic Pathways that Lead to Cancer*

Various processes are involved in the development of cancerous tumors, including but not limited to initiation and progression associated with alterations such as genetics and epigenomics (Kinzler *et al.,* 1996). According to Sandoval *et al.,* these epigenetic mechanisms are divided into four major categories: modifications of histone proteins after translation, DNA methylation, chromatin remodeling, and non-coding RNAs. DNA methylation has been explored, for over 20years, to be a promising therapeutic route for cancer from epigenomics (Sandoval *et al.,* 2012).

Baylin & Ohm, (2006) explained that abnormal gene imprinting or silencing is another critical epigenetic pathway involved in tumorigenesis.

3.2.1. *DNA Methylation and Cancer*

Carcinogenesis is escorted by a large accumulation of methylated DNA in cells. These mutations are widely characterized by hypermethylation, and hypomethylation of genomes of several 5'cytocine-phosphate-guanine" (CpG) islands actively traversing gene enhancers. Interestingly, these modifications occur timely in carcinogenesis. DNA methylation can pave the way for the discovery of cancer biomarkers for early detection and treatment (Warwick *et al.,* 2019).

The methylation of DNA is often characterized as the elevator of overexpression of tumor carcinogenesis. Many studies have shown that the eruption of DNA methylation can lead to several diseases, including cancer. Hypermethylation and hypomethylation are believed to be the conceivable focus of epigenetic cancer research.

The emanation of anomalies in DNA methylation results in the proliferation of cancer cells, which are believed to be implicated in oncogenesis. Hypermethylation in cancer cells is systematically experimental in transcriptional regulation, where it plays an important role in reinforcing the development of cancer genes, including "tumor suppressor genes." DNA methylation canyons, otherwise called DNA methylation valleys, are found hypermethylated in cancer cells.

Additional aspects of cancer cells are genome-wide hypomethylation, which causes inconsistent durability in chromosomes and steers oncogenes' overexpression (Warwick *et al.,* 2019).

3.2.2. *Histones and Chromatin Modification in cancer*

Epigenetic histones and chromatin modification in cancer remain one of the most important research areas, particularly in cancer biology. Histone modification plays a fundamental role in cancer prognosis. Due to the improper targeting of histone-modifying enzymes, abnormalities in histone modification are repeatedly detected in cancer, which is depicted in individual gene boosters (Kurdistani, 2007)

Histone modification occurs due to three different forms of modifications: modifiers, methylation, acetylation, and ubiquitination, which are the major players in histone modification and are involved in cell development and cancer (Alaskhar *et al.*, 2018).

3.2.3. *Histone Methylation*

Histone methylation is a significant regulator in transcriptional factors which impact the chromatin structure and exploit transcriptional factors that join in initiation and elongation and affect RNA. Histone methylation involves the developmental and differentiation stages in human cells. However, the accumulation of divergent histone methylation leads to the progression of tumorigenesis (Zibo & Ali, 2019).

3.2.4. *Acetylation*

Acetylation is the most systematic transformation that prevails in biological procedures. Lysine acetyltransferases (HATs) and lysine deacetylases (HDACs) are the two main enzymes controlling the proportion between acetylation and deacetylation. Several studies have shown that modulation of acetylation restoration of protein has been substantiated to be an aptitude treatment of cancer. Changes in the transcriptional status of numerous HDACs have been found in different types of cancer, such as gastric and colorectal cancer (Shiqin *et al.,* 2020).

3.2.5. *Ubiquitination*

Ubiquitination of histone transpires in histone proteins such as (H2A and H2B). Histone modification involves transcriptional activation and gene silencing, which also impacts the structure of chromatin (Zibo & Ali, 2019). Ubiquitination and deubiquitination are believed to be implicated in the legislation of metabolic programming in cancer cells. Ubiquitination is the most crucial form of post-translational mutation and enzymatic function that carries out various biological movements. When dysregulated, ubiquitination and deubiquitination can govern many diseases, including cancer (Tianshui Sun. *et al.*, 2020).

4.0. Epigenetic Modifications in Different Cancer Types

4.1. *Epigenetics of Breast Cancer*

Breast cancer (BC) is the most frequent neoplasm that affects women globally, accounting for 11.7% of all oncologic diagnoses and 6.9% of all cancer deaths (Bray *et al.,* 2018). Four main subtypes of BC have been described. These include the HER2-enriched tumors, which make up 12–20% of all breast cancers, the Luminar A tumor, which makes up 40% of all breast cancer, the Luminar B tumor, which makes up 20% of all breast cancers, and the Basal-like tumors, which make up 15% of all breast cancers (Johnson *et al.,* 2021). Breast Cancer occurs due to abnormal changes at both the genetic and epigenetic levels (Gulab *et al.,* 2022). As a result, various molecular, cellular, and biological pathways involved in breast cancer development are affected by epigenetic changes such as DNA methylation, histone modification, nucleosome remodeling, and RNA-mediated gene targeting (Dawson *et al.,* 2012). There has been research that suggests epigenetic deregulations may have a part to play in cancer drug resistance and stemness (Pasculli *et al.,* 2018); therefore the role of dysregulated methylation of genes and regulatory proteins in the pathogenesis of human cancers, including BC, is becoming more apparent (Gulab *et al.,* 2022). As a result, methylation-analysis assays are now being used in research to develop unique BC techniques for diagnosis and treatment (Jool *et al.,* 2018, Salas *et al.,* 2020; Tang *et al.,* 2016). Several underlying mechanisms for how DNA methylation causes cancer pathogenesis have been investigated. For instance, hypomethylation of SEPTIN7, TRIM27, LIMD2 and LDHA has been connected to BC infiltration and proliferation (Salas *et al.,* 2020). Additionally often methylated in BC patients are the APC, RARB, GSTP1, DAPK, and SFN genes (Tang *et al.,* 2016). In addition, methylation-induced aberrant expression of Claudin-6 (CLDN6) encourages breast cancer by enlisting MeCP2, deacetylating H3 and H4, and altering the structure of chromatin (Liu *et al.,* 2016). DNA methylation dysregulation is a vital reversible epigenetic mechanism linked to BC pathogenesis through gene expression dysregulation (Gulab *et al.,* 2022). Several studies have shown that deregulated DNA methylation causes changes in gene expression, which leads to the development of clinicopathological features of BC and thus has excellent potential for diagnosis and treatment (Masood *et al.,* 2016, Fleischer *et al.,* 2017 Jin *et al.,* 2019). Abnormal epigenetic modifications of antioxidant gene expression have also been well-studied and linked to the development of BC and therapeutic challenges. Triple-negative breast cancer (TNBC) has been shown to have widespread genome-wide hypomethylation compared to other BC subtypes. A comprehensive genome-wide DNA-methylation analysis recently revealed that clustering of circulating tumor

cells (CTCs) induces metastasis and progression in BC. Deregulated methylation binding sites for stemness and proliferation-associated transcription factors such as OCT4, NANOG, SOX2, and SIN3A are responsible (Gulab *et al.,* 2022). Worner et al. proposed that deregulated DNA methylation is one of the critical underlying events associated with the transformation of mesenchymal stem cells into tumor-forming cells in BC development (Worner *et al.,* 2019).

4.1.1. *Non-coding RNAs*

Evidence exists to prove that numerous epigenetic mechanisms, including DNA methylation, play an essential role in regulating the expression and function of non-coding RNAs (ncRNAs), which are essential for preserving biological homeostasis. Changes in these mechanisms result in abnormal ncRNA expression, which promotes BC pathogenesis (Gulab *et al.,* 2022). Shi et al. recently inspected the epigenetic silenced miR-133a-3p and found a link between this ncRNA and BC metastasis and stemness features by upregulating mastermind-like transcriptional coactivator 1 (MAML1) (Shi *et al.,* 2019). It has also been discovered that abnormal DNA methylation of the tumor suppressor microRNA-874 facilitates breast cancer development. It is also linked to lymph node metastasis (Zhang *et al.,* 2017). Another study found that abnormal DNA methylation contributes to BC pathogenesis by dysregulating 12 ncRNAs, including miRNA124, 125b, 127, 132, 137, 148a, 191, 193a, 203, 34b, 375, and 9 (Pronina *et al.,* 2017).

4.2. *Epigenetics of Lung Cancer*

Lung cancer is the most significant cause of cancer-related deaths worldwide, with an estimated 5-year survival rate of 18%. Because of late diagnosis, lung cancer is inoperable in 80 percent of patients. This belief has resulted in very slight increases in survival rates (Quintanal-Villalonga and Molina-Pileno, 2019). In the United States, around 220,000 people are diagnosed with lung and bronchus cancer each year, with tobacco use being the leading cause (Siegel *et al.,* 2018). Non-small cell lung cancer is the most frequent type (NSCLC; 85 percent). The most common kind of NSCLC is lung adenocarcinoma (LUAD), which accounts for 40% of all cases, followed by lung squamous cell carcinoma (LUSC) (25%), and large cell carcinoma (which accounts for 10% of all cases) (Zappa & Mousa, 2016).

4.2.1. *DNA Methylation*

RASSF1A (Ras association domain family 1A) is a potential effector proteins and tumor suppressor genes that controls Ras's apoptotic effects through GTP-dependent binding to Ras (Shi *et al.,* 2019). RASSF1A has also been linked to the DNA damage response and the activation of cell cycle arrest via cyclin D1 buildup (Shivakumar *et al.,* 2002). RASSF1A hypermethylation has previously been found to have early diagnostic and prognostic relevance in lung cancer (Begum *et al.,* 2011). CDKN2A (cyclin-dependent kinase inhibitor 2A) was given many names by different researchers (pl6INK4, p16INK4A, CDK4I, MTS1, and p16) but it is now recognized as CDKN2A by the Human Genome Organization Gene Nomenclature Committee. Due to its crucial functions in cell cycle progression, cellular senescence, and the development of human malignancies, CDKN2A has been one of the most extensively investigated proteins in recent decades (Shi *et al.,* 2019). The tumor suppressor CDKN2A prevents CDK4 and CDK6, two D-type cyclin-dependent kinases, from phosphorylating the retinoblastoma (RB) tumor suppressor protein and causing cell cycle arrest (Tam *et al.,* 2013). In primary NSCLC, homozygous deletion, promoter hypermethylation, and less commonly point mutations are the main causes of CDKN2A inactivation (Kraunz *et al.,* 2006). Previous research found that the CDKN2A promoter region was methylated at rates ranging from 20% to 70% in lung cancer (Shi *et al.,* 2019). These genes are often methylated in lung cancer and are essential in the disease's biological progression.

4.2.2. *Non-coding RNAs*

Non-coding RNAs (ncRNAs), among which are long non-coding RNAs (lncRNAs), short microRNAs (miRNAs), and circular RNAs (circRNAs), regulate gene expression at multiple levels in disease, including epigenetic memory, transcription, RNA splicing, editing, translation, and even cancer (Shi *et al.,* 2019). According to new research, several ncRNAs play critical roles in developing lung cancer. These compounds have been discovered as oncogenes or tumor suppressor genes that play a role in carcinogenesis and tumor progression (Yi *et al.,* 2019).

The most extensively researched ncRNAs in lung cancer are microRNAs (miRNAs). MiRNAs control a wide range of biological activities, including the control of the cell cycle, cellular expansion, proliferation, differentiation, apoptosis, metabolism, brain patterning, and aging (Uddin & Chakraborty, 2018). While certain miRNAs have the ability to behave as oncogenes, stimulating tumor growth, others can serve as tumor suppressor genes. MiR-21, for example, is

typically overexpressed in NSCLC. Overexpression of miR-21 promotes carcinogenesis by targeting negative regulators of the RAS/MEK/ERK pathway such as SPRY1, SPRY2, SPRY3, BTG2, and PDCD4. APAF-1, FASLG, PDCD4, and RHOB are also implicated in apoptosis (Hatley *et al.*, 2010).

Table 1: MicroRNAs alteration in various human cancers

MicroRNAs	Target gene(s)	Alterations	Cancer type	Reference
miR-124	CDK6	Downregulation	Colorectal cancer	Wang *et al.* 2013; Ponomarev *et al.,* 2011
miR-34b/34c	p53 network, CDK6, E2F3	Upregulation	Colon cancer	Bommer *et al.,* 2007; Hiyoshi *et al.,* 2015
miR-372, miR-373	RAS, p53,CD44	Upregulation	breast cancer	Eyking *et al.,* 2016;
miR-21	PDCD4, PTEN, TPM1, RECK, TIMP3, BCL2	Upregulation	Glioblastoma, breast, lung, prostate,	Xue *et al.,* 2016; Wang *et al.,* 2019; Stafford *et al.,* 2022
miR-155	RHOA	Upregulation	breast, colon, and lung cancers	Zhang *et al.,* 2019; Xue *et al.,* 2016; Gao *et al.,* 2018
miR-126, miR-124	CRK1, PIK3R2, SPRED1, VCAM1	Downregulation	Breast and lung cancer	Li, 2019; Liu *et al.,* 2022; Zhao *et al.,* 2017
miR-218, miR-145	PXN	Downregulation	Breast, lung and prostate cancer	Zhang *et al.,* 2015;
miR-145	ER	Downregulation	Colon and breast cancer	Shen *et al.,* 2019; Nakhaie *et al.,* 2020; Spizzo *et al.,* 2010
miR-9	FGFR	Downregulation	Breast, pancreatic cancer	Tavakolian *et al.,* 2020; Wang *et al.,* 2019; Nowek *et al.,* 2018
miR-148	TGIF2	Downregulation	Colorectal,	Sun *et al.,*

			melanoma, pancreatic cancer	2019; Wang *et al.,* 2019

BCL2: B-cell lymphoma 2 protein; CD44: cluster differentiation 44; CDK6: cyclin D kinase 6; CRK1: Cdc2-related kinase1; ER: estrogen receptor; FGFR: fibroblast growth factor receptor; PDcD4: programmed cell death 4; PIK3R2: Phosphatidylinositol 3-kinase regulatory subunit beta; PTEN: phosphatase and tensin homolog; PXN: paxilin; RAS: rat sarcoma; RECK: reversion inducing cysteine rich protein kazal Motif; RHOA: Ras homolog gene family member A; SPRED1: sprouty-related, EVH1 domain containing 1; TGIF2: Transforming growth-interacting factor 2; TIMP3: Tissue inhibitor of metalloproteinase-3; TPM1: tropomyosin 1; VCAM: vascular cell adhesion molecule.

4.3. *Epigenetics of Colorectal Cancer*

Colorectal cancer (CRC) is a form of cancer that begins in the gastrointestinal (GI) tract's colon or rectum section of the large intestine. They are assumed to develop by a well-defined multi-step sequential carcinogenesis process in which a series of genetic changes accumulate (Mamlouk *et al.,* 2020). CRC is the third most prevalent cancer diagnosed globally. In 2020, CRC contributed to 9.4% of cancer deaths and 10% of cancer incidence worldwide (Sung *et al.*, 2020). According to the American Cancer Society, there will be 151,030 new cases of CRC and 52,580 deaths in the United States in 2022 (Siegal *et al.*, 2022). Although there have been recent advancements in diagnosis and therapeutic methods, there has not been significant increase in CRC patients' survival rates (Zhou *et al.*, 2022).

4.3.1 *Driver genes*

In a recent study on CRC mutations, 468 colorectal tumors were examined for 1321 genes linked to human cancers. KRAS, TP53, APC, SMAD4, FBXW7, BRAF, TCF7L2, PIK3CA, GNAS, CBX4, ADAMTS18, TAF1L, FAM123B, CSMD3, ITGB4, LRP1B, and SYNE1 were identified as the subset of 17 genes with identical mutation frequencies that are most frequently mutated in CRC. These genes are listed in decreasing order of mutation rate (Schell *et al.*, 2016). Six of these genes, APC, KRAS, BRAF, PIK3CA, SMAD4, and TP53 have been identified as CRC driver genes, with APC, KRAS, PIK3CA, and p53 being the most often mutated. While PIK3CA mutation and loss of SMAD4 and P53 are late events in the transition from normal epithelium to an adenoma, APC, KRAS, and BRAF mutations are early events. Late events that allow tumor cells to penetrate adjacent organs and spread, turning the adenoma into a carcinoma, are caused by mutations or epigenetic silencing (Raskov *et al.,* 2020).

Microsatellite instability (MSI) and metastasis are both substantially correlated with mutations in the APC, TP53, KRAS, and to a lesser extent, SMAD4 genes (Haigis, 2017). While SMAD4 and distant metastases were very weakly correlated, KRAS and p53 mutations were strongly associated with distant metastases among 39,313 CRC patients, even though the KRAS mutation is an early event in CRC carcinogenesis. APC, BRAF, and PIK3CA did not correlate with any distant disease (Huang *et al.,* 2018). The KRAS or APC mutations typically co-occur or variations in TP53 or both. While BRAF, ITGB4, CBX4, CSMD3, SYNE1, FBXW7, and TAF1L are strongly connected with MSI but not with metastatic disease, this trio is highly deadly and predicts poor survival (Raskov *et al.,* 2020).

4.4. *Epigenetics of Prostate Cancer*

Globally, prostate cancer (PC) remains highly prevalent among males (Macedo-Silva *et al.,* 2021). Although the mortality rates are relatively low, this malignant disease is the number two most common cancer in men because of widespread screening of prostate-specific antigen (PSA) (Bray *et al.,* 2018; Sung *et al.,* 2021). Based on estimates by Globocan, 14 million new cases of PC were diagnosed in 2020 (Sung *et al.,* 2021).

4.4.1. *DNA Methylation*

The observation of the effect of DNA methylation on gene expression in cancer found changes that result in the silencing of proximal genes and the impact of modification of methylation on the DNA's ability to bind histones, transcription Factors, and chromatin-associated protein complexes (Greenberg *et al.,* 2019). Massie et al. (2017) reported a comprehensive meta-analysis of DNA methylation in PC. The meta-analysis further proved how typically methylated genes such as GSTP1 and RARβ provided a mechanistic rationale linking metabolic changes to possible changes in methylation patterns during prostate carcinogenesis (Massie *et al.,* 2017). Lee et al. (1994) reported one of the earliest findings that linked the alteration of DNA methylation patterns to PC. Their research showed that GSTP1 was not expressed in PC tissue because of the hypermethylation of the promoter. In benign prostatic hyperplasia (BPH), the GSTP1 promoter gene is not methylated, and its expression is seen in normal basal epithelial cells (Lee *et al.,* 1994). Due to the GSTP1 expression being lost in prostatic intraepithelial neoplasia (PIN), luminal cells, and glands of the PC tissue, it has been suggested for use in the early carcinogenesis tissue marker (Lee *et al.,* 1997 and Martignano *et al.,* 2016). Afterward,

changes in DNA methylation patterns during prostate carcinogenesis have been revealed through whole-genome methylation studies (Mahapatra *et al.*, 2012, Zhao *et al.*, 2020; Kron *et al.*, 2013). The studies confirmed the hypermethylation of GSTP1 and showed other promoters of genes such as RARβ, HIF3A, and HAAO have tumor suppression, response to hypoxia and microsatellite stability-related function, respectively, and were hypermethylated in PC in contrast to benign tissue (Mahapatra *et al.*, 2012, Kim *et al.*, 2011 and Kron *et al.*, 2009). Also, studies of PC tissue showed hypermethylation of HOXD3, a gene involved in the signaling of BMP7 TGFβ, which has been reported to suppress metastatic potential (Kron *et al.*, 2009 and Kukkonen *et al.*, 2021). Changes in DNA methylation have been linked with PC carcinogenesis, progression, and treatment resistance (Kukkonen *et al.*, 2021).

Table 2: Histone modification genes altered in various human cancers

Histone Deacetylases	Alterations	Cancer Type	Reference
HDAC1	Upregulation Downregulation	Gastric carcinomas, colon cancer, breast cancer, Prostate cancer. Colorectal cancer	Losson *e al.,* 2016; Cao *et al.,* 2017
HDAC2	Upregulation	Multiple gastric carcinomas, colon cancer, gastric cancer, pancreatic cancer.	Losson *e al.,* 2016; Goutas *et al.,* 2021; Singh *et al.,* 2018
	Mutation	Colon cancer, endometrial, gastric cancer	
HDAC3, HDAC7, HDAC8	Upregulation	Colon cancer	Biswas *et al.,* 2018; Goutas *et al.,* 2021
HDAC4	Upregulation	Prostate.	Losson *e al.,* 2016; Singh *et al.,* 2018
	Downregulation	Lung and colon cancer	
	Mutation	Breast and colorectal cancer	
HDAC5	Upregulated	Colon cancer, AML	Stypula-Cyrus *et al,* 2013; Wang *et al.,* 2020
HDAC6	Upregulation	Breast, ovarian cancer	Losson *e al.,* 2016; Singh *et al.,* 2018

SIRT1	Upregulation	Prostate cancer	Singh *et al.,* 2018; Chen *et al.,* 2021
	Downregulation	Colon cancer	
SIRT2	Downregulation	Glioma, gastrc cancer	Singh *et al.,* 2018; Zhang *et al.,* 2020
SIRT3	Upregulation	Breast cancer	Singh *et al.,* 2018
SIRT7	Upregulation	Breast, thyroid carcinoma	Singh *et al.,* 2018

HDAC: histone deacetylase

4.5. *Epigenetics of Skin Cancer*

Currently, there are three different forms of skin cancer, each called by the location of the cancerous cells. They are melanoma, squamous cell carcinoma, and basal cell cancer (from basal intracellular melanocytes) (Fijalkowska *et al.*, 2021). Clinical categorization, epigenetic change, and management of these skin tumors vary (Sang & Deng, 2019). Melanoma is the most lethal kind of skin cancer due to its aggressiveness and great propensity for growth (Chen *et al.*, 2022). The most considerable mutational burden of any cancer form is found in melanoma, predominantly due to UV exposure. The 3′ base of the pyrimidine might undergo a C-to-T change due to UVB. The G-to-T change brought on by UVA-related oxidative damage is another classic UV characteristic mutation (Shen *et al.,* 2020). In order to better understand the pathophysiology of melanoma, epigenetic modifications have recently gained increased interest (Giunta *et al.,* 2021). Tumor cells' epigenetic profiles are actively changed during the whole course of melanoma development, particularly regarding DNA methylation and histone acetylation (Chen *et al.,* 2022). Additionally, disruption of epigenetics may have a significant impact on several essential traits of tumor cells, including cell division, stemness, invasion, and migration, as well as metabolism and tumor immunology (Jin *et al.*, 2020, Li *et al.*, 2020, Diener *et al.,* 2021, Falahat *et al.,* 2021). Thus, mechanistic knowledge of these mechanisms would aid in thoroughly illuminating melanoma etiology and offer more readily available and druggable options for establishing new treatment modalities (Chen *et al.,* 2022).

4.5.1. *DNA Methylation*

One epigenetic characteristic of melanoma is abnormal DNA methylation, and several studies indicate that it is crucial for developing and spreading the disease. There are three primary

recognized transferases in mammals that regulate DNA methylation (DNMT1, DNMT3a, and DNMT3b), all of which are overexpressed in human tumor cells (Nishiyama & Nakanishi, 2021). The DNMT3a and DNMT3b enzymes are primarily responsible for the methylation of novel CpG sites. DNMT3a has modest expression levels in many body tissues but has a remethylating impact and keeps tissue cells remethylated. Simultaneously, lowering DNMT3a expression can somewhat limit melanoma tumor cell spread and proliferation (Sang & Deng, 2019). Hypomethylation of the whole genome can activate an oncogene, whereas hypermethylation of CpG islands can block tumor suppressor genes. As a result, hypomethylation of the total genomic DNA and hypermethylation of CpG islands can lead to cancer (Locke *et al.,* 2019). So far, genome-wide aberrant DNA methylation has been documented in cell lines and human melanoma tumors. It is linked to the disease's cellular and functional properties, as well as its clinical pathology. Many malignancies, including melanoma, have been identified as having focal DNA hypermethylation of tumor suppressor gene promoters (Guvenc *et al.,* 2021).

PTEN, p16/14, and RASSF1A (Ras association domain family 1, isoform A) silencing in melanoma has received much attention (McKenna and Garcia-Gutierrez, 2021, Huang *et al.,* 2021, Davis *et al.,* 2019). PTEN phosphatase transforms PIP3 (phosphatidylinositol phosphate) to PIP2, hence inhibiting PI3K activity and reducing PI3K/AKT pathway activation (Yang *et al.,* 2019). Due to the presence of hypermethylated CpG islands in the PTEN promoter, PTEN can potentially serve as a tumor suppressor independent of PI3K (Bazzichetto *et al.,* 2019). Many studies have found that PTEN methylation is a major predictor of poor survival in melanoma patients (Micevic *et al.,* 2017). Mirmohammadsadegh et al discovered that 62 percent of melanoma serum samples tested positive for PTEN promoter methylation (Mirmohammadsadegh *et al.,* 2006).

p16 is a protein encoded by the CDKN2A locus that plays a crucial role in halting the cell cycle at the G1/S checkpoint by inhibiting CDK4 and CDK6 and activating RB (Maner *et al.,* 2020). The CDKN2A locus also encodes p14, which binds to MDM2 and prevents it from activating p53 ubiquitination and targeting it for proteasomal destruction (Janani *et al.,* 2021).

Two areas of the RASSF1A CpG island were methylated in 44 metastatic melanoma tumors and 11 melanoma cell lines in an early investigation on aberrant melanoma and DNA methylation.

Overall, RASSF1A was hypermethylated in 55% of melanoma tumors, which was associated with the gene's decrease in expression (Spugnardi *et al.*, 2003). RARB2, MGMT, DAPK, and RASSF1A were examined for methylation in 20 primary melanomas, 86 metastatic Melanoma, and 15 cell lines in a subsequent investigation. In basic tumors, RASSF1A was methylated in 15% (3/ 20) and metastatic samples; it was methylated in 57% (49/86) of cases, suggesting that the amount of methylation may be related to the advanced stage (Hoon *et al.*, 2004). 5-aza-20 deoxycytidine therapy of melanoma cell lines resulted in the re-expression of the RASSF1A gene, indicating that CpG island hypermethylation in the promoter and concurrent gene silence may be reversed. Human melanoma frequently exhibits hypermethylation of cancer-associated genes with transcriptional abnormalities in their promoter regions (Micevic *et al.*, 2017).

4.5.2. *Histone modifications*

DNA methylation and histone alterations have a strong connection, as they both affect each other during nucleosome remodeling and gene expression regulation. Histone modification may help direct DNA methylation patterns and provide long-term stability of gene repression (Zhuang *et al.*, 2020). It will therefore be possible to better understand the current DNA methylation data by researching histone alterations in melanoma. The abnormal histone acetylation is hypothesized to have an impact on the pathogenesis of melanoma by interfering with the same mechanisms implicated in mutations and the hypermethylation of CpG islands (van den Hurk *et al.*, 2012).Gene expression analysis in melanoma demonstrates that reversible deacetylation of lysine residues in local histones by HDACs causes the loss of the expression of tumor suppressor genes (Florenes *et al.*, 2004). Despite the limited information on the post-translational changes of histones, HDAC inhibitors are being considered for the treatment of melanoma (Martí *et al.*, 2012). Specific pro-apoptotic proteins including Bak, Bim, and Bax, which are members of the BCL-2 family, are known to be downregulated when histones are hypoacetylated (Zhang *et al.*, 2004). Recent research has demonstrated that PIB5PA suppresses tumor growth and is often downregulated in melanoma. Histone deacetylation via histone hypoacetylation, which is mediated by binding to the transcription factor Sp1 on the promoter of the PIB5PA gene, is responsible for the downregulation of PIB5PA in a percentage of melanomas. (Ye *et al.*, 2013). In a zebrafish melanoma model with the BRAFV600E mutation, histone methyltransferase SET Domain, Bifurcated 1 (SETDB1) upregulates melanoma and hastens tumor growth. SETDB1

promotes the repression of target genes by catalyzing the trimethylation of histone H3K9 (Ceol *et al.*, 2011).

4.6. *Epigenetics of Pancreatic cancer*

Pancreatic cancer is an aggressive illness typically asymptomatic at first but patients develop symptoms similar to chronic pancreatitis (Yang *et al.*, 2021). This characteristic makes early detection difficult, contributing to the high recorded mortality (5-year survival: ~7%), making it the most terrible and lethal of all cancer kinds (Sung *et al.*, 2021; Liu *et al.*, 2019). Pancreatic neuroendocrine tumor (PanNET) and pancreatic ductal adenocarcinoma (PDAC) are the two most prevalent kinds of pancreatic cancer. The exocrine portion of the pancreas is where PDAC, which makes up 85% of cases, begins. PanNET, on the other hand, has a far lower possibility of occurring and targets the endocrine portion of the pancreas (Mostafa *et al.*, 2017, Rawla *et al.*, 2019). Discovering novel indicators and directing the development of combination treatments can be possible by understanding the epigenetic landscapes that cause pancreatic cancer (Ciernikova *et al.*, 2020). PDAC formation and progression are significantly influenced by many vital epigenetic pathways, including DNA methylation, post-translational changes of histone proteins, and non-coding RNAs (Syren *et al.*, 2017, Tchio Mantho *et al.*, 2017).

4.6.1. *DNA Methylation and hypomethylation*

Nearly 80% of pancreatic cancer cases exhibit increased DNMT1, which catalyzes parental methylation and effective offspring transformation, resulting in hypermethylation and opening the door for DNA hypermethylation as the most common epigenetic change in pancreatic cancer (Ciernikova *et al.*, 2020). Overexpression of DNMT1 was reported to be responsible for silencing key tumor suppressor genes such as p16, PENK, and RASSF1 (Hong *et al.*, 2018). Several studies reported that CDKN2A/p16INK4 was the first tumor suppressor gene inactivated due to aberrant hypermethylation in their promoter region, leading to silencing the CDKN2a/p16INK4 gene and causing pancreatic cancer (Khan *et al.*, 2021).

Preproenkephalin (PENK), found on chromosome 8q23-q24, encodes the neuropeptide precursor protein met-enkephalin and inhibits the opioid growth factor receptor by interacting strongly. According to reports, met-enkephalin can slow the growth of various human malignancies, most notably pancreatic cancer (Cullen & Cascella, 2022). According to Comb *et al.*,

hypermethylation of CpG islands in the PENK promoter considerably lowers its expression (Comb & Godman, 1990). In their examination of pancreatic ductal adenocarcinoma samples, Noriyoshi et al. found that 14 of 15 (93 percent) patients had abnormal hypermethylation in the PENK promoter. As a result, abnormal methylation of the PENK promoter may be a factor that promotes cellular proliferation and tumor development (Fukushima *et al.,* 2002)

Protocadherin 10 (PCDH10) is a tumor suppressor gene on chromosome 4 q28 that encodes a protein involved in various critical cellular processes. While protocadherin is generally recognized for its capabilities in cell-to-cell adhesion, it also retains several other critical capabilities, including growth regulation and signal transmission (Mah & Weiner, 2017). Transcriptome sequencing has been used to study protocadherin in pancreatic cancer, which typically exhibits abnormal methylation. According to recent research, PCDH10 is abnormally hypermethylated in 14 out of 23 (60.9 percent) individuals with pancreatic adenocarcinoma, which lowers the expression of PCDH10 and is linked to a bad prognosis for the disease (Curia *et al.,* 2019).

In comparison to typical pancreatic ductal cells, it was discovered that the genes SERPINB5, CLDN4, SFN, LCN2, TFF2, and S100P were overexpressed. Numerous changes in cell cycle progression, proliferation, differentiation, or adhesion resulted from this (Ciernikova *et al.,* 2020). Hypomethylation and, thus, abnormally elevated gene expression might be epigenetic markers for pancreatic cancer (Neureiter *et al.,* 2014).

4.6.2. *MicroRNAs*

Deregulated miRNAs promote the production of proto-oncogenes or reduce the expression of tumor suppressor genes which, among other things, cause PDAC carcinogenesis (Yang *et al.,* 2018). miRNA-21, miRNA-196a, miRNA-27a, miRNA-146a, and miRNA-200a were the five most elevated miRNAs, according to Hong and Park's investigation of the expression profiles of miRNAs in PDAC tissues. However, the studied cohort showed the greatest downregulation of miRNA-96, miRNA-217, miRNA-141, miRNA-20a, and miRNA-29c (Hong & Park, 2014). Due to miRNA's stability in blood, it is possible to correlate a specific miRNA's plasmatic level with the disease's stage, prognosis, or aggressiveness (Yonemori *et al.,* 2017, Wang *et al.,* 2018). Specific miRNA expression profiles correlated with distinct stages of PDAC may be biomarkers, prognostic indicators, and therapeutic targets (Daoud *et al.,* 2019). Patient-derived xenografts

and pancreatic tumors have recently been found to significantly alter miR-200a, miR-200b, miR-200c, miR-141, miR-429, and miR-205 expression. The findings suggest that miR-429, in particular, a member of the miR-200 family, may function as a tumor suppressor gene in PDAC (Diaz-Riascos *et al.*, 2019).

Table 3: DNA methylation gene changes in various human cancers

DNA methylatransferase	**Function**	**Alterations**	**Cancer Type**	**Reference**
BRCA1, BRCA2	DNA repair, maintaining genome integrity	Hypermethylated	Lung cancer, ovarian cancer	Hatziapostolou and Illiopoulos, 2011; Pfeifer, 2018
APC	negative regulator of the Wingless/Int (WNT) signaling pathway	Hypermethylated	Lung, Breast, Colorectal, pancreatic, prostate, gastric cancer	Hatziapostolou and Illiopoulos, 2011; Pfeifer, 2018
ATM	recognizing the damaged DNA, recruitment of repair proteins, transcriptional regulation, and apoptosis activation	hypermethylation	Colon, glioma, gastric lymphoma	Kermi *et al.,* 2019; Sriramulu *et al.,* 2019
CDH1	E-cadherin, cell adhesion	Hypermethylated	Breast, Lung, Prostate, colon cancer	Kulis and Esteller, 2010; Eroglu *et al,* 2018
CDH13	H-cadherin, cell adhesion	hypermethylated	Breast, Lung, colon	Kulis and Esteller, 2010; Kontic *et al.,*2018
$p16^{INK4a}$	CDK4 inhibitor, control of cell-cycle G1 progression	hypermethylated	Breast, Lung, Prostate, colon	Kulis and Esteller, 2010; Bhatia *et al.,* 2022
PTEN	Negatively regulating AKT/PI3K signaling pathway,	hypermethylated	Breast, melanoma	Thuy *et al.,* 2017
RASSF1A	Cell cycle arrest/regulator	hypermethylated	Breast, melanoma	Thuy *et al.,* 2017
MBD2	Transcription	Upregulation,	Prostate cancer,	Das and Singal,

	repression	Mutation	colon cancer, lung cancer	2004
MBD3	Transcription repression	Upregulation, Mutation	Colon cancer, lung cancer	Das and Singal, 2004
MBD4	DNA repair, glycosylase domain, repair of deaminated 5-methylC	Upregulation, Mutation	Colon cancer, gastric cancer, endometrial cancer	Das and Singal, 2004
Kaiso	Transcription repression	Upregulation	Colon, intestinal, lung cancer	Das and Singal, 2004

APC: adenomatous polyposis coli; ATM: ataxia-telangiectasia mutated gene; BRCA: Breast cancer gene; CDH: Cadherin; DNMT: DNA methyltransferase; MBD: methyl-CpG-binding domain; MeCP: PTEN: Phosphatatse and tensin homolog

5.0. Breakthrough of cancer therapeutics based on epigenetics

Epigenetic aberrations are reversable as such; researchers are looking more into innovative medicines that reverse their effect. Evidence from recent studies shows that, during malignant transformation, genetic and epigenetic pathways interact and benefit from one another (Hatzimichael & Crook, 2013). Biomarkers and therapies are the two main areas of epigenetics' clinical application that have the most attention (Benetatos *et al.*, 2010).

Cancer biomarkers: Methylated DNA has a number of characteristics that make it a desirable molecule for the use of biomarkers. Such properties include:

- They maintain their stability in biofluids including blood, urine, saliva, etc.
- Neoplasia-specific CpG methylation is acquired during malignant transformation.
- Automation is easily possible for the methods used to detect methylated DNA (McDevitt, 2012).

Individualized cancer therapy is one of oncology research's main objectives. The search for genes whose transcriptional suppression impacts susceptibility to chemotherapy drugs is still ongoing (McDevitt, 2012).

5.1. *Epi-miRNA and DNA methylation in Cancer Therapy*

Epi-miRNAs are microRNAs that regulate the genes that are involved in DNA methylation. They control the activities of the three significant DNMTs, including the proteins that bind to cytosine in the promoter site. Since the tumor suppressor gene is an essential therapeutic approach in cancer treatment, epi-miRNA must not be down-regulated. Therefore, this control of DNA methylation in a cancerous cell result in the inhibition of cell proliferation, invasion, metastases, and apoptosis (Karimzaseh *et al.*, 2021)

5.2. *Chromatin Modifications in Cancer Therapy*

The chromatin conformation at a particular locus determines the resulting transcriptional expression and that locus. Such transcription locus must be approachable and usable to transcriptional machinery and modulatory factors. Polycomb family repressors, trithorax family activators, and chromatin remodelers all impact the chromatin network (Piunti & Shilatifard, 2016). Gene mutation of these factors has pronounced consequences on epigenetics. Deregulation of this gene mutation can result in tumor formation. For instance, the permissive state of chromatin is associated with Transcriptional Factors (TFs) and chromatin modifiers such as p300 and MLL. Gene mutations in CBP/p300 and MILL1 inhibit healthy commitment of regulatory sites in leukemia. In brief, abnormal restrictive and permissive states of chromatin can lead to tumorigenesis (Winter & Bernt, 2017).

Some of the challenges of these biomarkers have been translating the findings into clinically functional tests to inform the optimal development of anti-cancer drugs. It is still improbable that a single gene methylation test would provide enough information to advise the care of a specific patient, and it is more likely multiple gene panels will be necessary (Datta *et al.*, 2009).

6.0. Recent Advances and Future perspectives in Cancer Epigenetics

Widely accepted is the belief that dysregulation of the epigenetic state plays a significant role in cancer development. However, the capacity of scientists to therapeutically target the epigenome is still in its infancy, and different researchers are working on this actively. Few epigenetic treatments have been authorized for use by patients, despite the fact that several are thought to have entered clinical trials. It has proven difficult to produce medications thought to target various epigenetic regulatory processes, such as histone methylation/demethylation. Because

epigenetic treatments are thought to occasionally impair the immune system or even promote a malignant phenotype, the most promising emerging cancer medicines that target epigenetic processes are those that are combined with immunotherapy (Cheng *et al.,* 2019).

In the developing field of cancer prevention and therapy, finding less cytotoxic medications is presently seen as a viable and beneficial strategy to rectify epigenetic abnormalities. Additionally, unlike genetic errors, epigenetic aberrations may be reversible and present promising prospects for the development of innovative cancer treatments that might activate epigenetically repressed tumor-suppressor genes (Aasheim *et al.,* 2015; Hathaway *et al.,* 2012).

It has been discovered that for the creation of novel anti-cancer therapies, epigenetic proteins and protein markers are suitable targets. The FDA's clearance of demethylating drugs and histone acetylase inhibitors for the treatment of specific types of lymphomas served as justification for this. However, one of the main disadvantages is that they are non-selective and their adverse effects are unknown (Fenaux *et al.,* 2009).

6.1. *DNA methyltransferase inhibitors/ demethylating agents*

These act to inhibit the functions of DNA methyltransferase. The most widely used are azanucleosides azacytidine and decitabine, approved for use in myelodysplastic syndrome. It is, however, disheartening that clinical trials with these agents in solid tumors did not have the same results. Also, decitabine is known to cause grade 4 neutropenia in most patients. Decitabine combined with carboplatin has been reported to cause myelosuppression toxicity. The activity of demethylating agents in solid tumors is limited due to their low incorporation into cells which are known to proliferate relatively slowly (Soriano *et al.,* 2007)

6.2. *Histone Deacetylase inhibitors (HDACi)*

For histone modification, HDAC catalyzes the removal of acetyl groups from lysine residues in the histones. Five different types of HDAC that also exist function as transcriptional repressors (de Ruijter *et al.,* 2003). It is believed that HDACi were discovered before HDAC. The first inhibitor of histone deacetylase discovered was sodium butyrate which induced methylation and was followed by trichostatin, an antifungal agent. Valproic acid, an antiepileptic was identified. Valproic acid has been found applicable in patients with hematological malignancies (Raffoux *et al.,* 2010)

Based on their structures, HDACi can be divided into chemically distinct subgroups, and these are:

- Aliphatic acids, e.g., Phenylbutyrate and valproic acid.
- Benzamides e.g. entinostat
- Cyclic peptides, e.g., Romidepsin
- Hydroxamates, e.g., Vorinostat.

The first FDA epigenetics-approved drugs were vorinostat and romidepsin. In 2006 and 2009, respectively, they were utilized as a second line of therapy for the management of cutaneous T cell lymphoma that was progressing or recurring, and various HDACi are now being examined in phase II-III studies. It appears that they would need logical combinations in order to counteract the HDACi's natural tendency to trigger the tumor-progression gene (Liu *et al.*, 2012). An example of such a combination is givinostat combined with hydroxyurea in patients with polycythemia vera. It is known to target the cells harboring the JAK2 V617F mutation selectively. Also, the second generations of HDACi, like ACY-1215, are more selective and currently entered clinical trial settings (Santo *et al.*, 2012). Recently, there has been evidence that combining HDACi and DNMTi may significantly increase clinical efficacy and avoid unavoidable toxicities. An example is a combination of azacytidine, a DNMTi, and entinostat, an HDACi. The combination produced clinical responses in pretreated metastatic non-small-cell lung cancer patients (Juergens *et al.*, 2011). Another recent advance is in the determination of the reversibility of adverse epigenetic marks in cancer inflammation that can be prevented by specific diets, natural photo chemicals, or lifestyle changes because synthetic epigenetic drugs have a high potential to be highly toxic and lack the specificity of actions. Additionally, research has shown that diet and diet-derived polyphenols of plant origin have strong anti-cancer chemopreventive effects in people by altering the activities of epigenetic machinery like HDACs. This is because these compounds have anti-inflammatory, antioxidant, phytohormonal, and homeostatic effects on cancer cells (Heightman, 2011).

For usage in clinical settings, many therapeutic compounds that can alter epigenetic pathways in different disease situations are being considered. Going forward, additional studies of the therapeutic approach to epigenetic therapy are required. The procedure of amalgamating

different epigenetic therapies (e.g., the combination of epigenetic therapy and chemo or immunotherapy), believed to have a synergistic effect in killing cancer cells, is now believed not to be selective for target cells. By turning on gene expression, normal cells may develop cancer. More knowledge of the molecular processes controlling these epigenetic modulators will make it easier to create medications that are more focused and efficient (Egger *et al.,* 2004).

6.3. Limitations faced by Scientists

Genetics and epigenetic modifications are critical to all stages of diseases, and the misregulation of genes involved in cancer's fingerprints has been linked to epigenetic silencing (Jones & Baylin, 2007; Feinberg *et al.,* 2006). Despite the potential of epigenetic therapy, most current treatments lack precision. Due to their ability to produce global demethylation by passive demethylation or DNMTs trapping, epigenetic medicines that target DNA methylation or DNMTs exhibit significant cytotoxicity. The drugs on the market are not appropriate for targeting the gene or cell-type-specific epigenetic deregulation (Cherblanc *et al.,* 2012). For these epi-drugs, the main difficulty will be converting the efficacy at nanomolar-scale concentrations in vitro into clinical use that is both well-tolerated and effective (Lu *et al.,* 2020). The creation of drugs that target crucial TSGs that are aberrantly repressed is an option that could lessen the unwelcome cytotoxicity and has already demonstrated some early encouraging outcomes (Yao *et al.,* 2003). However, these drugs have failed to produce a noticeable response in clinical testing. For example, MG98, at doses between 25 and 76nM, was found to reactivate silenced TSGs by downregulating DNMT1 effectively in several cancer cell lines. It also had an inhibitory effect on proliferation (Amato, 2007). It has already been proposed that side effects, such as allelic imbalance or genomic instability, may develop after several years of therapy, making it much more challenging to discover (Sharma *et al.,* 2009).

Another problematic issue is the development of acquired resistance to some epi-drugs. Like with any medicine, cellular processes affecting drug uptake and efflux, drug metabolism, and modifications to the drug target can all potentially alter efficacy by leading to the emergence of resistance (Ropero *et al.,* 2006). An alternate strategy for answering this question would be to use response biomarkers to identify people especially susceptible to epigenetic therapy. The current challenges are designing new anti-cancer drugs that are conjugated with cancer-specific biomarkers and choosing a site-specific delivery mechanism that can maximize therapy efficacy

and reduce toxicity (Roberti *et al.,* 2019). For example, The PRC2 inhibition in the BETI-resistant AML cells suggests that the BETI-targeted c-Myc expression may be recovered (Rathert *et al.,* 2015). In triple-negative breast cancer (TNBC), hyperphosphorylation of BRD4 also contributes to BETi's resistance (Alqahtani *et al.,* 2019).

Another major issue is tissue dependence and subpar results in solid tumors. Before considering treatment, it is crucial to confirm targets in a tissue-specific way because the effect of HDAC inhibition appears to be tissue-dependent (Lener, 2016). For instance, HDAC1 overexpression is associated with a worse prognosis for individuals with lung and pancreatic cancer but is associated with a higher chance of surviving breast cancer (Gao *et al.,* 2010). Additionally, solid tumors have only yielded unsatisfactory results, despite the beneficial effects of HDAC and DNMT inhibitors for hematological neoplasms.

6.4. *Promising aspects that try to overcome these limitations*

Demethylating drugs may offer unusual and surprising anti-cancer capabilities, according to Peter Jones. When he saw that, at low dosages, the chemical 5-azacytidine did not ruthlessly destroy cancer cells as other chemotherapy agents did, but instead softly prodded the cell into acting differently, he explored it as a potential chemotherapy agent (Jones, 1980). A clinical study of 5-azacytidine for patients with myelodysplastic syndrome (MDS), a disease that precedes leukemia, was initiated as a result of laboratory research on lung cancer and leukemia. It performed fantastically, and patient tests showed positive outcomes (Baylin *et al.,* 2014). In cancer cells, changes to the genome information are easily detected; few alterations determine how the cell functions. Cancer phenotype can revert to normal by reversing these mutations with drugs or gene therapy. Few alterations in the epigenetic modification in cancer can alter the cellular responses (Yuan *et al.,* 2019). The first clinical study of the combined demethylating agent and histone-blocking HDAC inhibitors was in patients with advanced lung, breast, and colon cancers. As is customary in early studies of anti-cancer medications, the treatments were not administered to individuals at the largest dose they could take. Low dosages were applied in its place. Instead of eradicating the cancer cells, as conventional chemotherapy drugs do, the aim was to destroy the cancer cells by altering their DNA. The medications were essentially employed by the researchers to shift the course of cancer cells, turning them into normal cells. The medicine destroyed cancer cells, but over time and at lower dosages, it reprogrammed

cancer cells to act like normal cells, providing a safer and longer-lasting cure for cancer (Jones *et al.,* 2008). The demethylating agent and HDAC inhibitor changed the gene expression of the cancer cell, making the cells that had previously been resistant to therapy now susceptible (Baylin *et al.,* 2014).

6.4.1. *Epi-Drug Therapy*

Epi-drugs targeting the epigenome of cancer have been developed over the years; each has shown promising results in clinical trials. Some of these drugs include Bromodomain and extra terminal inhibitors (BETIs), Non-Coding RNAs (ncRNAs) and DNA methyltransferase Inhibitors (DNMTIs) (Yuanjun *et al.,* 2020). The administration of several epi-drugs alongside chemotherapy and immunotherapy leads the way in cancer treatment due to its antitumoral efficacy and efficiency against drug resistance. “The impact of multiple epi-drugs treatments is based on the synergistic actions of epi-drug” (Yuanjun *et al.,* 2020).

Conclusion

In this review paper, we depict that epigenetic modification is believed to have enormous potential in cancer biology research. The accumulation of epigenetic changes and mutations in oncogenes and tumor suppressor genes (TSG) drives the progression of cancer cells. We also illustrate that all the epigenetic transformations such as DNA methylation, Histone, and chromatin modification, acetylation, and ubiquitination are associated with cancer, the mutation is one of the leading causes of cancer globally and epigenetics are the vanguard of this mutation due to some environmental factors, probing into epigenetics studies can magnificently unravel one of the global mysterious challenges of cancer.

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