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A Mini Review on Cancer Epigenetics

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Abstract: Cancer epigenetics is the study of epigenetic changes to cancer cells' DNA that don't involve a change in the nucleotide sequence but instead affect how the genetic code is expressed. The complicated disease of cancer is brought on by genetic and epigenetic changes in the regulation of cell division. Our knowledge of the molecular etiology of cancer has substantially advanced and also the discoveries in the fields of cancer genomics and epigenomics, which have improved our comprehension of the development and evolution of tumorigenic processes. The interaction between genetic and epigenetic mutations and their interaction with environmental factors, including our microbiome, that influences cellular metabolism and proliferation rates, must therefore be taken into account in any modern perspective on cancer research. Future genetic and epigenetic therapeutics as well as diagnostics and prognosis will all benefit from the integration and increased understanding of these processes. Here, we tried to give a general summary of the disrupted epigenetic processes in cancer and how they affect the beginning and development of the illness. In conclusion, we talked about how advanced experimental methods and computational tools, such as fresh methods for utilizing enormous data sets, could help us better understand and cure cancer.

Keywords: DNA, epigenetics, cancer, methylation, chromatin.

Review Paper

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1. INTRODUCTION

Angiogenesis induction, replicative immortality, sustained proliferative signals, growth inhibition evasion, resistance to cell death, invasion activation, and metastasis activation are characteristics of tumour formation in humans [1]. These characteristics are collectively referred to as the hallmarks of cancer. Carcinogenesis, however, begins when the activity and regulation of a collection of genes that support (oncogenes) or obstruct (tumor-suppressor genes) so cell differentiation are disrupted [2]. It has been demonstrated over time that there are numerous ways to cause the abnormal activation or deactivation of genes relevant to cancer. The most well- known process involves genetic changes that influence gene expression or interfere with the activity of the protein products those genes code for, such as polyploidy, deletions, inversions, polymorphisms, and translocations.

Today, our growing understanding of how epigenetic mechanisms govern the genome must be used to supplement the gene-centered perspective on cancer. The description and comprehension of epigenetic mechanisms for the regulation of gene expression have advanced significantly over the past three decades. As of right now, we can say that six interconnected processes make up epi- genetic regulation: a) histone post-translational modifications and histone variants; b) DNA methylation and demethylation; c) ATP- dependent chromatin remodeling complexes; d) the Poly- comb (PcG) and Trithorax (TrxG) complexes; and, more recently, e) non-coding RNAs and f) nuclear dynamics.

The interaction between genetic and epigenetic processes is one of this theory of cancer's most important components. Numerous experts, including Baylin and Jones, have suggested that neoplastic illnesses be treated while taking into account the strong connection between genetics and epigenetics [2, 3]. In this instance, at least three possible scenarios for the interaction of genetics and epigenetics in the regulation of gene expression in cancer may be imagined. Because transcription factors (TFs) can directly read genetic information at regulatory elements and recruit co-factors (co- activators or co-repressors), chromatin remodeling factors, and multi-protein complexes that modify chromatin and modulate gene expression programs, in the first scenario, mutations in TFs can result in changes in chromatin and gene expression. When genetic mutations in genes coding for epigenetic effectors (such as chromatin

remodelers, histone modifiers, and DNA methylases) cause their activity to be disrupted and can change gene expression, this is a second scenario for how genetics and epigenetics interact in cancer. Cancer can develop in specialized cells with pluripotent properties, such as adult or embryonic stem cells, which is an important factor to consider [4]. This is significant because, following fertilization, epigenetic patterns are generated that determine the fate of cells and our body's commitment to each cell lineage. In view of cellular therapeutics using the genome editing CRISPR-Cas systems, epigenetics therefore has a profound impact on cell differentiation and reprogramming processes that may indicate future therapeutic approaches. One of the most fascinating instances of how the physiological and environmental milieu can affect epigenetic regulation is shown in monozygotic twins [5, 6]. It follows that new approaches that take into account genetic and epigenetic characteristics are necessary for the study of cancer. Here, we discussed epigenetic mechanisms and how the improper control of them affects the development of cancer.

2. MECHANISMS OF EPIGENETICS

2.1 *DNA Methylation*

One of the most extensively researched epigenetic alterations is DNA methylation, which has been repeatedly linked to a number of medical disorders. For cell differentiation, development, genome integrity, and most significantly for the segregation of epigenetic characteristics, its regulatory function is extremely critical [7]. A contradiction was discovered after many years of DNA methylation research: in cancer, the same cells harboured hypomethylation in some genomic areas but, in contrast, localized hypermethylation within various genomic sequences. Biochemical methods have historically been used to show that cancer cells have hypomethylation by comparing their levels of 5-methylcytosine (5mC) to those of untransformed cells [8]. The abnormal increase in DNA methylation in tumour cells that also exhibit hypomethylation has been demonstrated over time to occur in a very localized genomic region, or so-called CpG islands, which frequently coincide with the promoters of genes, particularly those that regulate the cell cycle, such as tumor- suppressor genes [9, 10]. Because of this, large intergenic regions that are particularly rich in repetitive sequences and retrotransposon elements become de-compacted due to hypomethylation, which results in a general loss of heterochromatin and, as a result, in the induction of homologous recombination and extremely unstable genomic states linked to cancer [11, 12]. Contrarily, the so-called CpG-island methylator phenotype, which results in aberrant chromatin compaction and the suppression of gene expression, is brought on by the hypermethylation of CpG-islands [13].

DNA methyltransferases (DNMTs) carry out DNA methylation in a mechanistic manner. The nuclear proteins MeCPs and MBDs, which can bind to methylated DNA alone or in combination [14], can then recognize DNA methylation directly. Additionally, these nuclear factors for DNA methylation can collaborate with a wide range of co-repressors to attract histone deacetylases and methylases and produce a repressive chromatin conformation. MeCP and MBD mutations have been linked to aberrant chromatin silencing patterns in cancer cells [15]. The development and segregation of 5mC patterns following mitosis can also be affected by changes in DNA methyltransferases in cancer [16]. Without a doubt, DNA methylation plays a significant part in a number of independent and interrelated pathways in human cancer. These mechanisms of action contain elements of the epigenome that are not segregated by genetic differences.

2.2 DNA Demethylation

For a period of time, scientists discovered evidence of DNA demethylation, especially in the early phases of development. However, it was unclear whether other cell types experienced this phenomenon and whether it was an active or passive process. The ability to actively erase DNA methylation from the genome was first demonstrated once the Ten-Eleven Translocation dioxygenases (TET) and their enzymatic cascade were characterized. Three enzymes, designated TET1 to TET3, which are part of the TET family [17, 18], convert 5- methylcytosine (5mC) to 5- hydroxymethylcytosine (5hmC), which can then be oxidized to produce 5-formylcytosine (5fC) and 5-carboxycytosine (5caC). A crucial stage in the active demethylation process is the 5hmC. The AID/APOBEC family of enzymes can convert it into 5-hydroxymethyluracil (5hmU). The next step of the pathway that leads to the cytosine replacement and ultimately the DNA demethylation is reached when a base excision repair (BER) glycosylase like TDG or SMUG1 replaces 5hmU [19, 20].

The interaction between DNA methylation and demethylation is critical in both cancer and development. It is well- documented that over time and in association with ageing, there is a gradual loss of DNA methylation and gain of DNA demethylation, which disturbs a significant pattern of gene expression and genomic stability and causes various diseases, including cancer. It is well-known that the loss of this equilibrium can cause cancer at multiple levels.

3. Cancer, Histone Variants, and Histone Post-Translational Modifications

The chromatin structure's core is made up of histone proteins, which regulate the compaction and decompaction of the chromatin in a controlled manner. Additionally, chromatin landscapes with various roles, such as genomic stability, are produced by a mixture of

histone post-translational modifications [21]. Chromatin is arranged into a complex grid of nucleosomes, each of which is made up of an octamer of histones (H3 and H4, as well as H2A and H2B), with histone variations also present in some genomic areas [22]. Post-translational modifications (hPTMs) are applied to histones in a variety of ways, mostly at their N-terminal end, including acetylation, methylation, phosphorylation, ubiquitination, glycosylation, and sumoylation [23]. Because of this, histone modifications are linked to various chromatin states, enhancing chromatin accessibility and impacting the regulation of gene expression for many types of genes, including metabolic genes and, of course, genes linked to cancer [24, 25]. The vast majority of high-stone changes are reversible, which is an important feature of hPTMs and offers a bright future for therapeutic procedures. Cellular metabolism should be included as another factor in the histone modification modes of action. This relates to nutrient acquisition, but it also highlights the crucial role the gut microbiome plays in the metabolism of dietary nutrients, creating intracellular pools of metabolites that serve as the substrate for chromatin-modifying reactions, including but not limited to histone modifications [26]. Thus, a large number of metabolic intermediates operate as substrates or co-factors for epigenetic alteration, not only for hPTMs but also for nuclear factors, DNA, and even RNA [25].

The existence of somatic missense mutations in histones, which are connected to human illnesses and in particular, cancer, is another aspect of histones that hasn't been thoroughly studied [27]. This feature may have been deceptive because numerous genes are involved in the encoding of histones, and alterations in a single histone allele can go undetected despite the high rate of mutation. For instance, significant penetrance mutations in the H3 gene, which codes for the histone H3, have been found in uncommon pediatric brain and bone malignancies [28- 30]. Furthermore, hotspot mutations in rare child sarcomas including chondro-blastomas [30], and pediatric high-grade gliomas [30] that map to the directed N-terminal tail of histone H3 were discovered 20 years ago. There has lately been an effort to catalogue and characterize de histone missense mutations in various cancer types, including mutations discovered in all four core histones and their variations, as well as in the tail and globular domains [31]. Linker-histone, also known as histone H1, has also been linked to histone mutations [32]. In 30% of follicular lymphomas, between 30% and 40% of diffuse large B-cell lymphomas, and 50% of Hodgkin lymphomas, there is a mutation in the globular and C-terminal domains of the linker-histone, which bind nucleosomes and aid in chromatin compaction [33, 34].

Additionally, mutations in the histone H3 (H3K27) lysine 27 region have been linked to altered post- translational histone modifications in cancer cells, deregulation of the polycomb repressive complex, and changes in its repressive activity. Together, a number of histone mutation-related effects were discovered, including chromatin compaction, nucleosome destabilization, disruption of histone-DNA interactions, changes in chromatin-associated remodeling activities, and alterations in epigenetic signaling. Future research should take into account the fact that these so-called oncohistones, as determined by the mutations in them, are related to various cancer types [27].

The data pertaining to epigenetic changes, genomic stability, cell metabolism, and gene expression in cancer must be assimilated, in short [35]. Together, these details may contribute to a deeper comprehension of the mechanisms behind the development of cancer and the spread of its metastases, resulting in the development of new methods for the detection, prevention, and treatment of cancer.

4. ATP-Dependent Chromatin Remodeling Complexes

The coordinated action of the so-called ATP-dependent chromatin remodeling complexes is one of the most important factors connected to epi-genetic control. In order to cause nucleosome sliding, con- formational changes of nucleosomes, nucleosome displacement, and exchange of histone variants—all of which have positive and negative effects on the chromatin structure—these multi-protein complexes contain a central component with a helicase domain that needs energy from ATP hydrolysis [36].

The four families into which the ATP-dependent chromatin remodeling complexes are divided are as follows: a) The Chromodomain Helicase DNA (CHD) family of proteins, wherein some sub-units bind directly to methylated lysine at histone H3 to establish a close association with chromatin and can also be attracted to active enhancers labelled by histones H3K27ac and H3K4me1, as well as promoters rich in H3K4me3 [37], b) The SWI/SNF complex, which Rhabdoid tumours and other human cancers can emerge from mutations in the SWI/SNF subunits, for example [38- 40] c) The INO80/SWR family, which also consists of the SRCAP and P400/Tip600 complexes in addition to the INO80 complex. Interestingly, the SWR complex is also involved in the deposition of H2A.Z into nucleosomes; the INO80 complex induces nucleosome mobilization in an ATP- dependent manner; and the specific exchange of the high-stone variant H2A.Z at active gene promoter and enhancer elements. d) The ISWI family, which includes the two independent ATPase subunits SNF2H and SNF2L. The SWI/SNF subunits are not immune to mutations that cause human illnesses, including cancer, as was previously described [41- 42]. It has been shown that the genes encoding the various SWI/SNF subunits are altered in a large variety

of malignancies, but epigenetic flaws can also result in SWI/SNF miss-regulation in several cancer types [39]. As a result, many different cancer types, such as breast, ovarian, bladder, stomach, and liver cancers, are brought on by a confluence of genetic and epigenetic abnormalities [37]. Rhabdoid tumours, a rare and aggressive kind of cancer that typically develops in childhood, have historically been among the cancers that have been the subject of the most research [37- 43]. The SMARCB1 gene, which codes for the SNF5 subunit of the cBAF and pBAF subunits of the SWI/SNF complex, is genetically de-activated in rhabdoid tumours [41, 42].

In addition to the controlled exchange of histone variations in specific genomic areas, the ATP-dependent chromatin remodeling complexes work in close collaboration with histone modifications and nucleosomes to expose or occlude DNA regulatory sequences. A growing body of research indicates that genetic abnormalities affecting essential elements of multi-protein complexes, particularly in the ATPase sub-unit, are intimately associated to the development of cancer. Inappropriate regulation of these complexes can affect groups of genes in cancer.

5. Activating Trithorax Complex and the Repressive Polycomb

The Polycomb (PcG) and Trithorax (TrxG) groups of proteins are multiprotein complexes that control the chromatin accessibility of homeotic genes during development. They were first identified in Drosophila melanogaster as major regulators of homeotic genes [44, 45]. PcG proteins have also been linked to cellular memory as well as being important regulators of cell plasticity that support cell differentiation.

Across all meta-zoans, the repressive PcG complex is preserved. By triggering aberrant expression of homeotic genes, (often known as "homeotic transformations,) mutations in the Polycomb gene in the fruit fly cause embryonic transformation of anterior segments into posterior segments [44]. The Polycomb Repressive Complex 2 (PRC2, the initial complex) and the PRC1 complex (the maintenance complex) are the two sets of proteins that make up the PcG complex. The PRC2 is made up of the Embryonic Ectoderm Development (EED), the Suppressor of Zeste 12 homolog protein (SUZ12), and the Enhancer of Zeste Homolog 1/2 (EZH1/2), which have SET domains with H3K27me2/3 di- and tri-methyl methyltransferase activity (45,46). It's interesting to note that PRC2 is made up of other proteins and is divided into two unique complexes (PRC2.1 and PRC2.2) with different functions and specialties, despite the fact that their primary job is to insert the histone mark H3K27me3 into the chromatin regions they are targeting. It should be noted that certain transcription factors or co-factors are necessary for the recruitment of PRC2 to the site of action. Long non- coding RNAs (lncR- NAs), like HOTAIR lncRNA, have recently been shown to preferentially and specifically recruit PRC2 to the region of activity [47]. The Polycomb protein (Pc), one of the PRC1 maintenance complex's units, interacts with the histone H3K27me3 mark in order to support PRC2's action on the scene [45, 46]. The Polycomb group ring finger 1-6 (PCGF1-6) proteins and, more significantly, RING1A/Bm, an E3 ubiquitin ligase that mono-ubiquitinates histone H2AK119ub, are two additional subunits that make up PRC1 and contribute to the formation of both canonical and non-canonical complexes [49]. This reinforces the repressive effect of PcG.

PcG has been demonstrated to contribute to the aetiology of breast, prostate, and numerous other cancers [48, 50]. A lot of genes involved in gene transformation, including tumour suppressor genes, are chromatin-associated repressed, namely by the aberrant overexpression of EZH2 histone methyltransferase, which integrates the H3K27me3 histone mark (50). PcG and TrxG can affect gene expression and genomic stability at various levels because of their diverse activities. The relationship between non-coding RNAs and the recruitment of PcG and TrxG complexes to their site of action is also supported by additional evidence; nevertheless, this association has to be thoroughly studied from the standpoint of cancer development.

6. Extended Non-Coding RNAs

Biochemical evidence has indicated the existence of low- and high-molecular weight RNAs since the 1960s, but their characteristics and roles were unclear [51]. Non-coding RNAs have been re-evaluated and their many varied functions have been re-assessed in the post-genomic age [52- 53]. High-throughput sequencing technologies have opened up new perspectives on the world of non-coding RNAs, particularly on the enormous variability of long non-coding RNAs (lncRNAs) and their function in the development of cancer. Non-coding RNAs have been hypothesized as an extra layer of genomic and epigenomic regulation that interacts with proteins and nucleic acids in the nucleus and/or cytoplasm [53]. Small non-coding RNAs (sncRNAs; less than 200 nucleotides in length) and long non-coding RNAs (lncRNAs; greater than 200 nucleotides in length) are the two initial categories for non-coding RNAs. The transfer RNA (tR-NAs), messenger RNA (mRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs), which are involved in gene transcription, protein synthesis, and splicing, are some members of the first family of non-coding RNAs [54-56]. In more recent years, post-transcriptional and heterochromatin-related roles for microRNAs, piwi-interacting RNAs, and small interfering RNAs have been identified [57].

In this instance, the description concentrates on lncRNAs and their involvement in the development of various cancer types and carcinogenesis. LncRNAs are primarily produced by RNA polymerase II and exhibit orders-of- magnitude lower expression levels than mRNAs. They are also extremely cell type specific. They experience alternative splicing, which results in various isoforms with different secondary structures and, as a result, unique roles. The way they function is directly correlated to the molecules they interact with, especially other nucleic acids and a growing family of RNA-binding proteins (RBPs), which include individual proteins and protein complexes influencing DNA, RNA, and chromatin in various states, with coding and non-coding RNAs, and with the elements involved in transcription, imprinting control, splicing, translation, and protein stability, among many other processes. It's interesting to note that the transcription of lncRNAs regulates chromatin shape [58].

Examples of lncRNAs' contributions to epigenetic control are abundant. By interacting with important nuclear and architectural DNA-binding nuclear factors including YY1 and CTCF, as well as chromatin-modifying complexes like Poly-comb Repressive Complex 2 (PRC2), several lncRNAs contribute to chromatin dynamics [59- 61]. Telomeric Repeat-Containing RNAs (TERRA) can also draw the chromatin-associated proteins TRF2 and PRC2, which are involved in the development of specific heterochromatin at telomeres [62, 63]. Another illustration is the lncRNA AN- RIL, which, in senescent cells, recruits the repressive PcG complexes PRC2 and PRC1 to regulate the transcription of CDKN2A and CDKN2B genes in cis [64]. HOTAIR, which was first discovered in the HOX gene locus, is one of the most researched lncRNAs. By physically interacting with the PRC2 complex and LSD1, HOTAIR promotes chromatin compaction and gene silencing. It has been demonstrated that its overexpression happens in cancer metastasis and affects at least 800 genes' expression [65-66]. The enhancer RNAs are a different class of lncRNA that are involved in the creation of chromatin loops to bring active gene enhancers and promoters into close proximity as well as to attract or repel transcription factors [67]. Furthermore, another differential activity of lncRNAs favoring gene activation or silencing in cis via a decoy-mediated mechanism is the creation of RNA-DNA hybrid structures (R-loops) by complementary sequence [68, 69].

In many different medical conditions, including cognitive disorders, physiological flaws, syndromes, and of course cancer, it has been observed that non-coding RNAs and their enlarged activity signify a novel regulatory approach that is damaged. It is critical to differentiate the epigenetic regulatory systems linked to non-coding RNA in cancer since their mechanisms of action are still poorly known and there are so many variations. Their diverse and dynamic secondary structures, RNA-binding protein capacities to predict their effects in cancer, and amplification influence over sets of genes disrupting essential nuclear and cytoplasmic functions are all significant factors to be taken into account.

7. Cancer Chromatin

It has long been considered that the chromosomal segregation and genome organization during cell division are disturbed by the genetic flaws frequently identified in cancer. The underlying genetic information in our genome is impacted by polymorphisms, duplications, inversions, translocations, polyploidy, and many other chromosomal modifications [70]. The development of genome-wide sequencing techniques, along with experimental protocols based on the original chromosome conformation capture test (3C), and derived techniques that deepen our understanding of chromosome organization, has occurred during the past two decades [71]. Unquestionably, such topological organization affects not only cell differentiation but also gene expression [72, 73]. Today, it is evident that several classes of chromatin-driven cancers are affected by topological errors in the three-dimensional organization of the genome. Although it is outside the purview of this review to describe the three-dimensional structure of the genome, it is well known that cancer cells exhibit deformed cells, including the nuclear envelope, reprogramming of their genome and epigenome, reorganization in the nuclear space, and variations in DNA content [74, 75]. Cellular senescence and cancer cells have been shown to produce heterochromatin foci and loss of the so-called LADs, or lamina-associated domains, respectively [76]. Alterations to the nuclear lamina lead to the delocalization of heterochromatin associated with the nuclear envelope and the relocation of the LADs to the nucleoplasm, which has a profound impact on the epigenome and gene expression. Also, there are a number of structural differences at the three-dimensional level of genome organization that can influence the expression of a gene or set of genes that adopt a specific topological conformation. Genomic inversions, deletions, and duplications were among these changes [77, 78]. Additionally, structural differences in the epigenome can modify how enhancers and promoters communicate, thus affecting how genes are expressed. It's interesting to note that these mutations have been found to cause inappropriate overexpression of neighboring genes that are connected to them [79].

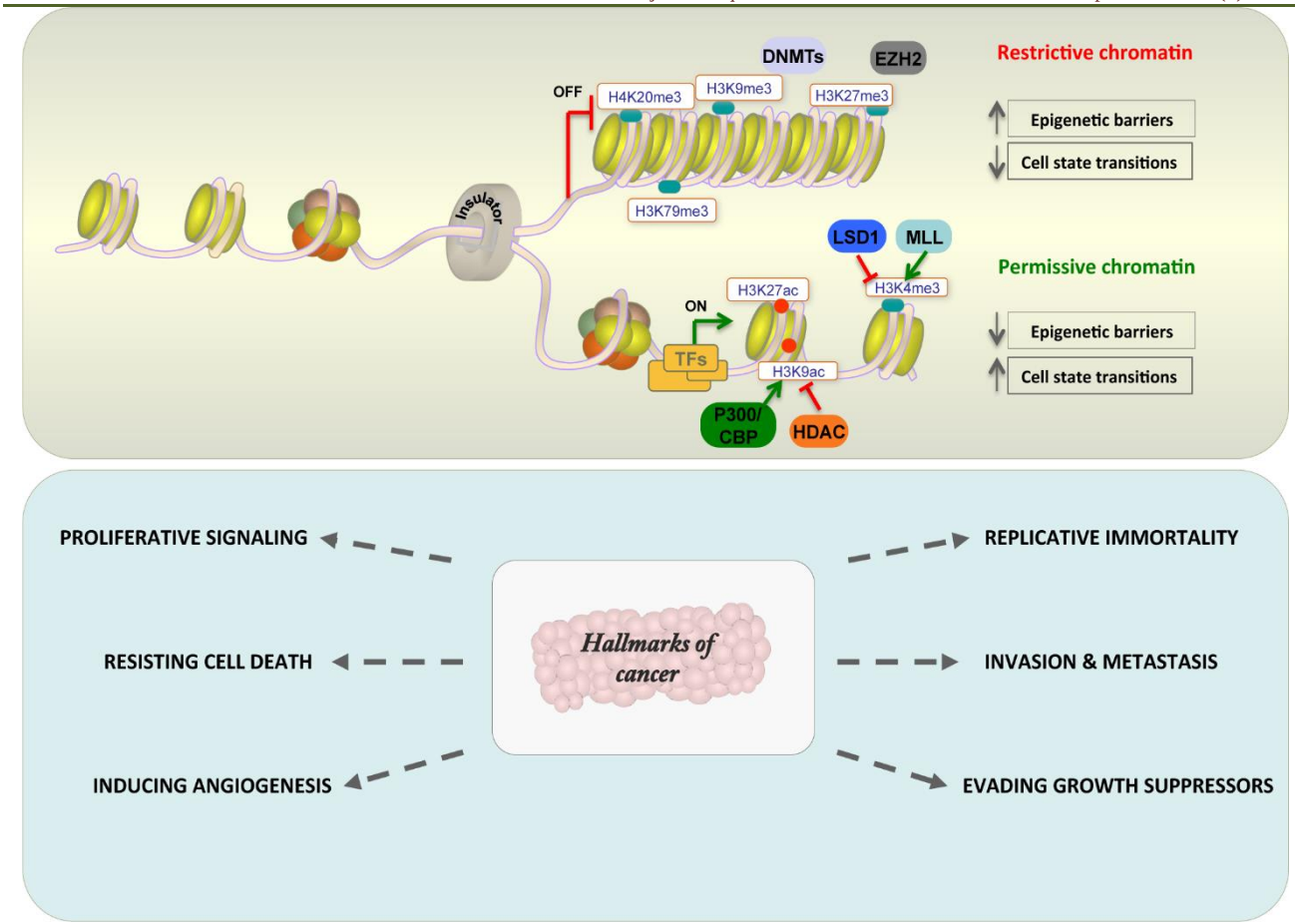

Figure 1: Gene expression and cancer-related characteristics are governed by chromatin structure. (Source: BMC)

8. Carcinogenesis in Animal Models

Results from in vivo carcinogenesis models can be used to forecast how the population's most vulnerable humans will react to genetic lesions or exposure to environmental carcinogens. These investigations can also pinpoint epigenetic biomarkers and shed light on the precise mechanisms behind tumour development. The analysis of epigenetic pathways that connect environmental exposures or genetic predisposition and cancer progression is made possible by a multitude of in vivo models of carcinogenesis. In these models, tissue-specific cancer is frequently induced through toxicant exposure or transgenic modification.

In epidemiologic research, significant exposures have been identified for certain cancers, such as lung cancer, but the early stages of carcinogenesis have not been fully characterized [80]. These lung carcinogenesis models have been used more recently to study the distinct epigenetic mechanisms that contribute to the advancement of lung cancer, such as elevated promoter methylation of the cell-cycle regulator genes p27 and p57 [81]. Through the use of animal models, epigenetic pathways have been clarified, leading to therapeutic treatments for the management of carcinogenesis. Demethylating drugs including 5-azacytidine, decitabine, and zebularine have been investigated in numerous animal models because they demethylate tumour suppressor genes, which is a typical feature of carcinogenesis. 5-azacytidine was administered to mice that had been given the ability to develop oral cavity cancer, and the mice's lesions were less severe than those of the control mice [82].

9. Treatments

The development and spread of cancer are influenced by epigenetic control of the proto-onco regions and tumour suppressor sequences by conformational changes in histones. A number of malignancies may benefit from medications that reverse epigenetic alterations [83- 85]. It is now clear that relationships between particular cancer histotypes and epigenetic modifications can help with the creation of new epi-drugs. Modifying DNA methyltransferase, histone acetyltransferase (HAT), and histone deacetylase (HDAC) has been the main focus of drug development [86, 87]. Azacitidine [88, 89], and decitabine are DNA methyltransferase inhibitors that selectively target the inverted methylation pattern of malignant cells [90- 91]. These hypomethylating medications are used to treat

myelodysplastic syndrome, a blood malignancy caused by atypical bone marrow stem cells, which is also known as MM [92]. These substances, which were previously believed to be highly toxic and inhibit all three types of active DNA methyltransferases, turned shown to be efficient when taken at modest doses, slowing the progression of myelodysplastic syndrome to leukemia [93]. After DNA methyl-transferase inhibitors have suppressed transcription, it has been discovered that treatment with HDAC inhibitors promotes gene reactivation [94]. It is permitted to use panobinostat in specific myeloma circumstances [95]. Histone lysine methyltransferases (KMT) and protein arginine methyltransferases (PRMT) are two more pharmacological targets being studied [96].

10. Epigenetic Therapy

Cancer epigenetic therapy has emerged as a promising and potential therapeutic for malignant cells. Because epigenetic inactivation selectively targets genes necessary for regulating cancer cell proliferation, it is a prime target for malignant cells. These genes must be triggered in order to inhibit tumour growth and make the cells more susceptible to cancer- curing treatments [97]. The goal of standard chemotherapy is to eradicate cancer cells from the body. Unlike epigenetic cancer, which causes epigenetic aberrations that may be corrected and allows cells to resume their normal functions, cancer caused by genetic abnormalities in cells is often persistent and nearly impossible to repair. The fact that the coding of the genes being silenced by histone and DNA modification is not being altered is thought to be the reason why epigenetic mechanisms can be reversed [98]. Combination therapy is a type of epigenetic therapy that uses more than one synthetic medication, such as an HDAC inhibitor and a low-dose DNMT inhibitor. These medications work in concert to attack the connection between DNA methylation and histone modification [99]. In terms of DNA methylation, the aim of epigenetic therapy for cancer is to reduce DNA methylation, which in turn reduces the silence of genes involved in tumour suppression [100].

11. SUMMARY

Through unchecked proliferation, malignant heterogeneity, and metastasis, the interaction between epigenetics and genetics play a crucial role in carcinogenesis and the advancement of cancer. To investigate and comprehend the genesis of cancer, it is important to take into account genetic errors on chromatin remodelers, epigenetic regulation, and disruption of genetic information. Cell metabolism adds another element to the multi- stage mechanisms that transfer regulatory signals to the genome but mostly cause epigenetic changes in the context of this complex cosmos. Several metabolic intermediates, including secondary metabolites, operate as substrates or co-factors for epigenetic modifications at this stage, including changes in the affinities of nuclear factors, DNA, or even RNA. For instance, it has been demonstrated that the Sirtuin (SIRT) family of NAD+-dependent deacetylates controls tumour growth through acetylation and deacetylation [101, 102]. The information and knowledge from various domains, including lifestyle, metabolism, microbiome, mitochondrial metabolism, genome organization and stability, and gene expression in carcinogenesis and cancer progression, must be urgently integrated in a coordinated manner. In order to completely comprehend epigenetic modes of action, more research is required. A greater understanding of the mechanisms underlying carcinogenesis, early detection and diagnosis, the progression to metastasis, prevention, and cancer therapy should result from the combination of this information and its integration.

Compliance with Ethical Standards

DISCLOSURE OF CONFLICT OF INTEREST: There is no conflict of interest regarding this paper.

Availability of Data and Materials: The data and materials used to support the findings of this study are publicly available.

AUTHOR CONTRIBUTION: All author contributed significantly to design and development of this work.

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