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DNA methylation, a key concept in epigenetics

Yuanlin Wu

Meixi Lake Middle School attached to Hunan Normal University

3394761283@qq.com

Abstract. DNA methylation, histone modifications, and CpG islands intricately regulate gene expression. Understanding these epigenetic mechanisms provides insights into cellular identity and how their dysregulation contributes to cancer development. Unraveling these complexities opens avenues for therapeutic interventions aimed at restoring normal epigenetic patterns in cancer cells. In light of the potential for epigenetic therapies to restore normal gene activity and enhance treatment outcomes, this work intended to present an overview of the state of knowledge about DNA methylation and its implications for cancer therapy.

Keywords: DNA methylation, epigenetics, DNMTs, CpG islands.

1. Introduction

Changes in genes and epigenetics are crucial for the onset and progression of cancer. Numerous studies have been conducted on the genetic alterations that contribute to cancer, including copy number variations, deletions, insertions, and recombination events in addition to DNA missense mutations [1]. It is now widely accepted that epigenetic disruptions cause carcinogenic characteristics to accumulate as well [2], such as changes in noncoding RNAs, nucleosome location, histone alterations, and DNA methylation.

To be more specific, DNA methylation is a kind of epigenetic mechanism that includes the addition of a methyl group(CH3) into the DNA molecule. It can inhibit the expression of genes by impeding the binding of transcription factors with DNA molecules.

As an example of how DNA methylation affects the initiation or development of cancers, DNA methylation can be involved in the promoter region in the DNA sequence. While gene body DNA methylation is frequently favorably correlated with gene expression, promoter DNA methylation may be adversely correlated with the state of gene activation [3]. If the tumor-suppressor gene is methylated, it is more likely to be suppressed, thus increasing the probability of cancer. Both mechanisms contribute to gene regulation, and the whole process is highly regulated. Different mechanisms, such as somatic mutations, insertions/deletions, and genetic and epigenetic changes of DNA methylation, can independently mute or activate one of or both gene alleles, then coordinating an impact on tumor suppressor genes and oncogenes throughout the human genome [4]. What's more, it's interesting to note that somatic mutations in epigenetic modifier genes have been found in large-scale cancer genome DNA sequencing analyses. This suggests that both of genetic and epigenetic systems or mechanisms also have the ability to reinforce one another in a mutually separate way.

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2. DNMTs - The key player of DNA methylation

DNA methylation is the chemical alteration of S-adenosine methionine (SAM) as a CH3 donor under the catalysis of DNA methyltransferases (DNMTs). It is the process of getting a methyl (CH3) group via covalent binding. It involves the addition of methyl groups to cytosine within CpG dinucleotides and is orchestrated by DNMTs, which means the DNMTs play important roles in the process of DNA methylation.

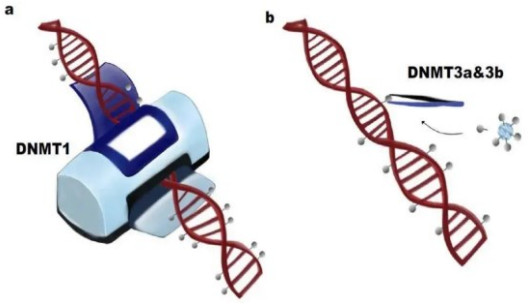

Figure 1. The roles of DNA methyltransferases in biochemistry.

(a) According to its definition, DNMT1 is a maintenance DNA methyltransferase. DNMT1 copies the current methylation pattern, favoring hemi-methylated DNA; (b) De novo DNMTs, such as DNMT3a and DNMT3b, transfer methyl groups donated by S-adenyl methionine (SAM) to unmethylated DNA to create new methylation patterns [33].

The primary players in this process are DNMT1, DNMT3A, and DNMT3B. DNMT1 ensures the maintenance of methylation patterns during cell division, while DNMT3A and DNMT3B contribute to de novo methylation, particularly in embryonic development.[1.] The development of an embryo is very similar to the developing stage of cancer. Genes critical for cell cycle and cell cycle progression can be interfered with by DNMT to encourage replication. In the process of DNMT participating in DNA methylation, cytosine (C) is the most common base of methylation, and C site methylation mainly occurs on the CpG sequence, which means CpG island is also an essential point in methylation.

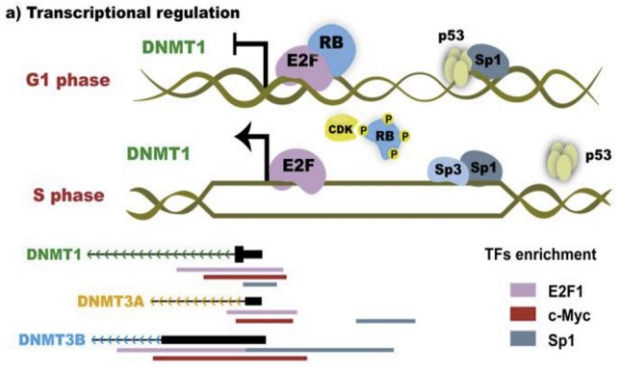

Figure 2. Transcriptional regulation and post-transcriptional modifications of DNMT1. (Adapted from Loaeza-Loaeza and Beltran)

When DNMTs move from phase G1 to phase S, their expression rises. Phase G1 sees pRB dephosphorylated and bound to E2F as a result of p53's interaction with Sp1. As p53 levels fall and CDK expression rises during replication, pRB that has been phosphorylated separates from E2F and p53 separates from Sp1, which makes it easier for DNMT1 transcription to be activated. In various cell lines examined for the ENCODE project, Sp1, E2F, and c-Myc transcription factors (TFs) are enriched in the promoters of DNMT1, DNMT3A, and DNMT3B.

There are a lot of regulators that regulate the DNMTs, for example, microRNAs (miRNAs). MiRNAs are a class of small RNA molecules that play a role in regulating gene expression in cancer by targeting

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specific mRNA molecules for degradation or inhibiting translation. In cancer, miRNAs are often dysregulated and can promote cancer development or act as tumor suppressor genes to suppress tumor growth. For instance, some important genetic expressions, such as the expression of tumor suppressor genes, may be restricted in the cancer cells due to unregulated DNMT expression, while this expression is carefully regulated in normal cells [30].

3. CpG Islands

CpG islands, characterized by high CpG content, are integral to epigenetic regulation. While the majority of genomic CpGs undergo methylation, CpG islands in gene promoters typically remain unmethylated, allowing for unimpeded gene expression. So, if the CpG island is methylated, the genes that follow it will be silenced. Defined by criteria such as a sequence length of 500 base pairs and a C + G content of more than 55% [5], CpG islands serve as epigenetic signposts guiding transcriptional regulation.

The distinct methylation status of CpG islands distinguishes them as essential contributors to chromatin accessibility and gene expression control. As an illustration, CpG residues in coding areas or gene bodies in somatic cells frequently lead to active spots for mutational, as seen in the inactivation of C to T transitions in the tumor suppressor gene TP53 [5]. Unlike non-CpG island promoters, which are predominantly methylated, CpG islands play a crucial role in maintaining an open chromatin state, essential for normal cellular function. For example, promoter CpG islands are usually hypomethylated in normal cells, but hypermethylated in tumor cells [6]. This reveals the relationship between the degree of methylation in promoter CpG islands and the risk of cancers.

4. Histone Modifications

Histone modifications, pivotal in shaping chromatin structure, constitute another section of epigenetic regulation. These modifications, involving the addition or removal of functional groups to histone proteins, significantly impact gene expression. The intricate interplay between DNA methylation and some specific histone modifications adds complexity to the epigenetic landscape.

Promoter DNA methylation is often related with histone H3 lysine 27 trimethylation (H3K27me3), which is associated with DNMT3A1, contributing to gene silencing. (figure 1.) [16]. Conversely, gene body DNA methylation correlates with histone H3 lysine 36 trimethylation (H3K36me3), facilitating gene expression [1]. So, for instance, in the case of cancer development, if the histone H3K27me3 is methylated, the promoter is also methylated to cause the subsequent suppressor or oncogene to be silenced. DNMT3B's association with H3K36me3 emphasizes the relationship between DNA methylation and histone modifications, revealing the regulatory mechanisms that can be also applied to cancer studies.

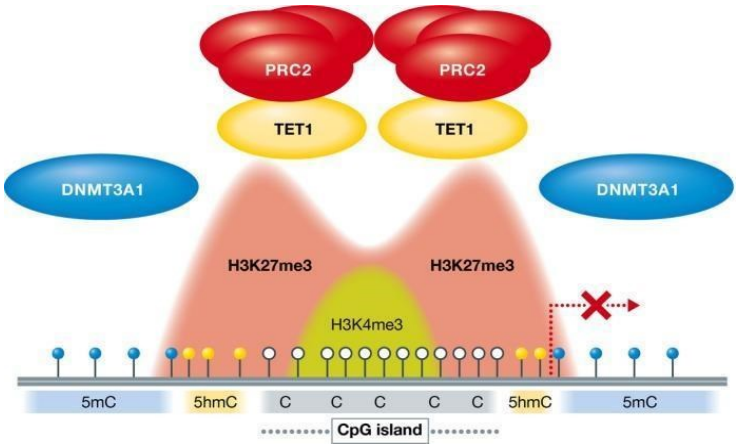

Figure 3. Polycomb targeting at bivalent hypomethylated CpG islands (CGI) is influenced by DNA methylation mediated by the de novo methyltransferase DNMT3A1 [16].

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Unmethylated transcriptionally inactive CGIs have been connected to methylated PRC2 targeting. Since H3K27me3 and DNA methylation can demonstrate mutual antagonism inside CGIs of mammalian genomes, CpG methylation inhibits the H3K27me3 histone mark that is catalyzed by PRC2 [29]. (PRC2, one of polycomb group proteins, which has histone methyltransferase activity, PRC2 inhibits gene expression through its histone H3K27 methyltransferase activity; TET1 is an enzyme that plays a positive role in DNA demethylation)

5. Dysregulation of DNA methylation

As mentioned above, there are different types of DNA methylation, and DNA methylation can occur in different sections of DNA, so in this section we will discuss two main categories of DNA methylation, hypermethylation and hypomethylation.

5.1. Hypermethylation

Hypermethylation is generally defined as an abnormal increase in the degree of methylation on DNA beyond normal levels. This state can lead to the silencing or inactivation of specific genes. In the case of cancer, we will pay particular attention to the effects of hypermethylation on tumor suppressor genes and oncogenes.

Together with genetic alterations like somatic mutations and deletions, hypermethylation in the promoter can also lead to gene silence, which is a secondary mechanism for the inactivation of the tumor suppressor genes (TSGs) [1].

On CpG island, the hypermethylation can also happen in some particular cancer species. For example, specific DNA hypermethylation of a subset, a certain small aera, of the gene areas, most remarkably the concordant promoter DNA, was observed in a subset of colorectal tumors. The term CpG island methylator phenotype (CIMP) refers to this condition [1,7].

Noncoding RNA (ncRNA) is a class of RNA molecules that don't code for any proteins in cells. They perform as a role that hold the post of various significant functions in the cells, including regulation of gene expression and helping to the maintenance of chromatin structure [8]. The hypermethylation can also happen to ncRNA. For example, DNA hypermethylation of miR-127, leads to downregulation of its expression and succeeding up-regulation of the BCL6 proto-oncogene, which promotes tumorigenesis [9,10].

5.2. Hypomethylation

In contrast to hypermethylation, hypomethylation is a state in which the level of methylation on DNA is lower than normal.

The majority of hypomethylation in DNA takes place in intragenic and intergenic areas. Repetitive and transposable elements, such as long interspersed nucleotide elements (LINEs) and short interspersed nucleotide elements (SINEs), are plentiful in these genomic regions [1,11]. LINE-1, can, for example, have a significant impact on gene expressions. The hypomethylation of this gene is known to be a predictor of tumor development and prognosis in a number of cancer types, including ovarian, bladder, renal, prostate, and melanoma [1].

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Table 1. This table suggested the significance of DNA methylation in various cancers and the abundance of the dysregulation discovered across different cancers, highlighting the potential of targeting DNA methylation as a potential therapeutic strategy.

cancer type	hyper(number)	gene	hypo(number)	gene	gene(not sure)	doi
GBM(gliobastoma muliforme)						(Della Monica and Cuomo)[17]
					IDH1	
					IDH2	
					O6-MGMT	
	1214		4353			(Ji and Zhao)[18]
LGG(low-grade glioma)		*ARL9*				(Tan and Zhang)[19]
					HTATIP2	(Dong and Deng)[20]
TCGA high-grade serous ovarian tumor	168				*BRCA1*	(The Cancer Genome Atlas Research Network)[21]
SKCM(skin cutaneous melanoma)	41					(Fu and Wu)[22]
		CLDN11				
		RASSF6				
		RASSF10				
		GPX3				
		MMP-9				
		SYNPO2				
		LINE-1				
LIHC(liver hepatocellular carcinoma)	11		14			(Fan and Tu)[23]
				ANAPC10		
				ANAPC4		
				BUB1		
				AURKA		
				CCNB1		
				ROBO1		
		AR				
		CCND1				
		BDNF				
breast cancer				*TSTD1*		(Muhamad Ansar and Thi)[24]
		GSTM2				(Ma and Li)[25]
		SOD3				
				ADAM12		
				LINE-1		
				KCNK9		
				YAP1		
					BRCA2	(Szczepanek and Skorupa)[26]
				RAD9		
				1-Oct		
				c-Fos		
				H-Ras		
				c-Myc		
		ERa				
		HOXA5				
		TMS1				
UCS(uterine carcinosarcoma)	2191		365			(Li and Xing)[27]
		NEFM				
		CLEC14A				
		EMILIN1				
					MGMT	(Mateusz Bujko and Kowalewska)[28]

6. Cancer therapy and future directions

As mentioned in the earlier section, DNMTs play a crucial role in methylation, so many studies have been conducted on DNA methyltransferase inhibitors (DNMTi).

At low dosages, DNMTis can activate genes that have been silenced, and at excessive levels, it can be harmful, or say cause cytotoxicity.[12] In a recent study, DNMTis can inhibit the formation of tumor endothelial cells and tumor angiogenesis,[14] which is a pretty interesting mechanism of the DNMTi because DNMTi can apply to any genetic modification. The huge potential of DNMTis could bring researchers some novel therapies for cancers.

DNA methyltransferase inhibitor zebularine and decitabine can significantly reduce tumor size in established tumor models by inducing re-expression and total demethylation of the p16 gene, as well as by cell cycle arrest and inducing apoptosis.[13] A second-generation prodrug, like guadecitabine, affects gene expression by inhibiting DNA methylation.[13] Guadecitabine caused dose-dependent demethylation and increase in p16 expression at both mRNA and protein level.[13, 32]

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On the other hand, it is also explored the possibility of combination therapy with immune checkpoint inhibitors. For example, in breast cancer, the potential of DNMTi combined with PD-L1 in the treatment of breast cancer has shown significant therapeutic effect: guadecitabine with anti-PD-1/L1 immunotherapy.[15.] By activating the anti-tumor immune response, DNMTi therapy increases MHC-I expression, attracts cytotoxic CD8+T cells, and activates the NFκB signaling pathway, thereby enhancing the response against PD-L1 therapy.[15.]

7. Conclusion

With more and more studies looking into DNA methylation, a large amount of evidence has presented another mechanism for DNA methylation regulation. It was suggested that DNA methylation mechanisms may be regulated by microRNAs (miRNAs), and that the regulation of these genes is critical for cancer occurrence and tumor progression.[30.] Under this circumstance, using DNMT inhibitors such as 5-aza-dC and 5-azaC could repair the expression of epi-miRNAs, a subset of miRNAs that target genes involved in epigenetic regulation.[30] Researchers believe targeting these EPI-miRNAs could be promising for cancer treatment.

This piece of work provides an introduction to the importance of understanding DNA methylation and its regulations, with an interest in the disruption of DNA stability in cancer. In the future researches in this field, it could be important to explain the specific mechanisms by which DNMTis interact with immune checkpoint inhibitors to enhance anti-tumor immunity. Additionally, exploring the role of other epigenetic regulators, such as histone modifiers, in combination therapies with DNMTis could provide a more comprehensive understanding of epigenetic-based cancer treatments. Moreover, investigating the potential of miRNA-based therapies, either alone or in combination with DNMTis, may offer novel approaches for cancer treatment by targeting specific epigenetic pathways.

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