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ROLE OF DNA METHYLATION IN CANCER DEVELOPMENT, PROGRESSION, AND THERAPEUTICS: A REVIEW

Imrana Tanvir[1], Tuba Binte Qasim[2], Samah S Elbasateeny[3] Saba Yasir[4], Nasir Saleem[5], Hanadi Talal Ahmedah[6], Amber Hassan[7], Muhammad Imran Naseer[8]

[1]Pathology Department, King Abdulaziz University, Jeddah, Rabigh Branch, Saudi Arabia
[2]Clinical Fellow, Academy of Surgery, Barking, Havering and Redbridge University Hospital NHS Trust, UK
[3]Department of Pathology, Faculty of Medicine, Zagazig University, Egypt
[4]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
[5] International Medical Centre, Jeddah, Saudi Arabia
[6]Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdul-Aziz University, Rabigh, Saudi Arabia
[7]PhD, Post-Doc, Department of Neurogenetics, National Scientific Neurological Institute IRCCS, Fondazione Mondino, Pavia, Italy
[8]Institute of Genomic Medicine Sciences (IGMS), King Abdulaziz University, Jeddah,
Saudi Arabia
Corresponding Author: Muhammad Imran Naseer,
Institute of Genomic Medicine Sciences (IGMS), King Abdulaziz University, Jeddah,
Saudi Arabia. Email: mimrannaseer@yahoo.com

ABSTRACT

Background: Epigenetic modifications play a fundamental role in the regulation of gene expression, with DNA methylation being one of the most critical mechanisms. Aberrant DNA methylation contributes to genomic instability and disrupts normal cellular processes, thereby promoting cancer development. Both hypermethylation and hypomethylation events are implicated in mutations affecting proto-oncogenes and tumor suppressor genes (TSGs), leading to malignant transformation.
Objective: This study aims to highlight the role of DNA methylation as a key epigenetic mechanism in cancer initiation and progression, and to evaluate its potential as a diagnostic and prognostic biomarker for early cancer detection and clinical decision-making.
Methods: A comprehensive analysis of recent scientific literature was conducted to examine the mechanisms of DNA methylation, including the roles of DNA methyltransferases in regulating gene expression, cell cycle control, differentiation, proliferation, apoptosis, and genomic stability. Emphasis was placed on studies investigating methylation patterns in proto-oncogenes, tumor suppressor genes, and their detectability in various body fluids.
Results: Recent studies demonstrate that cancer-specific DNA methylation signatures can be detected in body can be replaced by Emerging evidence indicates that tumor-specific methylation patterns can be detected in circulating DNA from body fluids, offering potential for non-invasive early cancer detection and prognostication.
Conclusion: DNA methylation represents a promising epigenetic biomarker for cancer screening, early diagnosis, and prognosis. Advances in DNA methylation profiling technologies hold great potential for identifying carcinomas at deep genetic and epigenetic levels. Furthermore, epigenetic biomarkers may play an essential role in guiding therapeutic strategies, supporting personalized medicine, and improving clinical outcomes in cancer management.

Keywords: DNA methylation; Epigenetics; Cancer biomarkers; Genomic instability; Tumor suppressor genes; Early cancer detection.

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide. Treatment remains challenging, and early detection is critical for improving clinical outcomes. The poor survival rate in cancer patients is mainly because of the lack of advanced diagnostic testing. We need more promising diagnostic biomarkers. Recent studies have proven that Cancer epigenetic modifications regulates genetic instability of the cells. DNA methylation is an epigenetic modification, not a direct mutational event. Kindly make a correction. DNA methylation contributes to carcinogenesis primarily through epigenetic regulation of gene expression, although it may indirectly promote

mutational events under certain conditions. DNA methylation abnormalities are associated with cancer, not always causative (1). This genetic reprogramming is due to the initiation or inhibition of multiple signalling pathways (2, 3). In the early development of cancer, epigenetic modifications happen, and focusing on these events promises invention of many early cancer detection biomarkers (4). DNA methylation plays a crucial role in gene expression. Alteration of DNA methylation patent leads to progression of cancer as DNA methylation have crucial role in gene expression (5). These facts make us believe that it will may be proved to be an important cancer biomarker.
Taken together, these findings strongly support the potential of DNA methylation based biomarkers as powerful tools for early cancer detection, prognosis, and disease monitoring. The stability, reversibility, and detectability of DNA methylation changes in various biological samples, including blood and other body fluids, further enhance their clinical applicability. Therefore, continued investigation into cancer associated DNA methylation signatures may lead to the development of more accurate, non-invasive, and clinically relevant diagnostic biomarkers, ultimately improving patient management and outcomes.

DNA METHYLATION ROLE IN CANCER DEVELOPMENT

Hypermethylation or hypomethylation of DNA leads to oncogenic properties in cells. This epigenetic alteration is due to epigenetic modifications. Hypermethylation is related to silencing of tumour suppressor gene, and this has been identified as a global reason behind oncogenes (6). In cancers, DNA methylation activates oncogenes and mainly effect suppressed genes (Fig. 1).
DNA methyltransferases (DNMTs) are a enzymes group, causing DNA methylation(7, 8). As a methyl group, they have S-adenosyl methionine which at five different positions of the pyrimidine ring, is transported into the cytosine. There are four different types of DNMTs in humans. These are DNMT1, DNMT2, DNMT3a and DNMT3b (8)

DNA HYPOMETHYLATION AND CANCER DEVELOPMENT

Epigenetic changes in human cancer cells are understood as changes when cells losses DNA methylation (m^5C residues replaced by unmethylated C residues). This was first described in 1983. This particular alteration of DNA methylation occurs in the entire genome in various tumor cells as compared to normal body tissues (7). Later it became evident that metastases is far more receptive to cancer-linked DNA hypomethylation as compared to the primary tumours. Subsequent multiple researches confirmed this overall frequent genomic hypomethylation in cancer cells as compared to normal control tissues (9).
Global researches have proved presence of hypomethylation in cancer cells which regulates growth factors and proto-oncogenes overexpression leading to uncontrolled genes, cell growth and metastasis(10). Initiation of DNA hypomethylation is multiple factoral, like e.g. tumour gene S100A4, PLAU, calcium binding protein initiates the process of DNA hypomethylation and this protein production modulates extracellular matrix functions, helping the invasion of the malignant cells. Thus tumor cells produce extracellular matrix protease which degrades extracellular matrix, promoting cancer cell metastasis. Protein regulated enzyme synthesis by S100A4, helps extracellular matrix to heal after any damage (11). The PLAU enzyme plays an important role in development of cancer and metastasis of the breast, prostate, and other cancers. In patients of breast carcinoma raised levels of PLAU are linked to an aggressive behavior, early invasion, metastasis and a worse prognosis (12) Insulin-like growth factor 2 (IGF2) influences tumor cell proliferation. Hypomethylation alters the IGF2 gene allele inside the tumor call which results ii cancer cell division boosting (12). The retrotransposons -based hypomethylation generates instability to cancer cell's genetics. Abnormal m5C regulation and methylation have been heavily looked into in recent research. It's role in the progression, metastasis, and therapeutic resistance of several types of tumors (13).
RNA m5c modification (5-methylcytosine modification is a chemical modification when in RNA cytosine residues get methylated at position, carbon 5. This modification is widely identified in various types of RNA like messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA) and non- coding RNA (ncRNA). These modifications plays vital role in different biological behaviours of cancer progression and tumor immune microenvironment remodelling by changing stability and translation efficiency of RNA(13).Table 2

DNA HYPERMETHYLATION AND CANCER

Several activated genes have shown DNA methylation which leads to epigenetic silencing and to instability of cancer cell genetics. Retinoblastoma tumour-suppressor gene (RB1) epigenetic modification creates the promoter part. Hypermethylation leads to silencing of a huge population of tumour suppression gene, which in turn regulates tumourigenesis in caners. Thus hypermethylation activity influences multiple-cell signalling in tumor cells. In several tumors, two p15 and p16 cell cycle-related gene hypermethylations were seen. Both regulate the phase G1 of the cell cycle. DNA repair system in tumor cells is effected by DNA hypermethylation. In DNA mismatch repair mechanism-based hypermethylation is related to gastric cancers and it also leads to the breakage of DNA stand in breast and

ovarian cancers. CDH1 gene (E-cadherin) silencing promotes cancer cell metastasis, and death-associated protein kinase 1 (DAPK1) gene silencing leads to escape of cancer cell apoptosis. Recent researches also highlighted an interesting fact that each cancer cell and type specifically carry an extraordinary pattern of DNA methylation (14).

DNA methylation-based Chromosomal instability, based on DNA methylation results in the initiation of the tumor metastasis. One of the major step in cancer metastasesis is epithelial-mesenchymal transition (EMT). Normally, epithelial cells are bound tightly to eachother by the extracellular matrix (ECM) which is a source of structural and biochemical support. ECM gets modified during the process of cancer development leading to cell motility thus tumor spreads to the different body parts. E-cadherin plays a key role in EMT, it is downregulated in carcinomas. DNA methylation and somatic mutation are few of the multiple steps that occur in order to regulate E-cadherin. E-cadherin is a cell adhesive molecule. E-cadherin epigenetic modification is because of the chromosome 16-based DNA methylation (15). Researches have also shown higher levels of DNA methylation of E-cadherin in oral lichenoid lesions (OLP) and oral lichen planus as compared to the non-inflamed epithelium (16). The 16q22.1 chromosomal location mutations is observed in mammary cancers. CpG hypermethylation in bladder cancer, p16 in renal and lung cancer. Furthermore, the methylation of 5′ CpG is seen in skin, liver, blood cancers. Gene methylation is related to the aggressive cancer development and progression.

DNA METHYLATION BIOMARKERS

DNA methylation biomarkers sound very promising tools for early cancer detection, accurate diagnosis, prognostic markers, new effective therapeutic options/monitoring and post treatment risk assessment. Development of DNA methylation biomarkers looks more promising for diagnostics (17). DNA methylation biomarker is also useful in updating about the mutation at the cellular level which provide relevant information regarding different stages of the disease progression. Lung cancer, squamous cell carcinoma (p16) hematological cancer (p15 also known as CDKN2B or INK4B) methylation based biomarkers were screened on liquid biopsy. MGMT promoter hypermethylation has shown association with squamous intraepithelial lesion and cervical cancer. uPAR gene hypomethylation can occur during the late stages of breast cancer. This can be caused by decreased DNA methyltransferase (DNMT) and increased demethylase (DMase) activity. These are due to the suppression of tumor suppressor genes and overexpression of tumor progression factors(18). uPAR gene hypomethylation leads to proto-oncogenes activation , which transform them into oncogenes. uPA gene promoter methylation status can be used as a biomarker used to predict the aggressive nature of the primary tumour (19)(Fig 2).

CANCERS, DNA METHYLATION PROFILING

DNA methylation profiling refers to the qualitative and quantitative analysis of methylation patterns at genome-wide or locus-specific levels. It has also its utilities in other fields like forensic and personalized medicine. For detailed cancer investigations DNA methylation based epigenetic investigation was globally conducted. 5-methylcytosine (5mC) generally identified in cancer was considered to be potential cancer biomarker. This important discovery unfolds the mistry of 5mC −5-hydroxymethylcytosine, 5-formylcytosine and 5-carboxylcytosine, which draw attention worldwide to this a new dynamic discovery of epigenetic signatures. Multiple different technologies are being worked on and some are already developed for evaluation of DNA Hypomethylation and hypermethylation(19, 20).

Different technologies used to analyze DNA methylation are:

1- **ELISA:** It is simple and rapid. It can be used to any specific DNA methylation at global level before doing next-generation sequencing.
2- **Mass spectrometry:** It is used to determine the level of DNA methylation
3- **HPCE (HIGH-PERFORMANCE CAPILLARY ELECTROPHORESIS):** It do faster quantification of DNA methylation as compared to any other method which are HPLC (HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY) based.
4- **Microfluidic technique:** This technique use capture protein for methylated DNA binding domain
5- **Pyrosequencing:** It is a reliable method, high-throughput and quantitative way to analyze DNA methylation at several CpG sites.
6- **Reduced Representation Bisulfite Sequencing (RRBS):** This assay gives information regarding any single-nucleotide, single-allele resolution for a specific genomic region.
1- **EpiTYPER DNA Methylation Analysis:** it is a precision-targeted technology which at specific CpG sites measures DNA methylation levels.

2- **Infinium Methylation Assay:** This technique uses Illumina technology and bisulfite conversion to detect the level of methylation in more than 285,000 sites in the mice genome.
6- **Nanopore Sequencing:** It is third-generation sequencing which is based on electrical signals to identify base sequences based.
7- **MeDIP Sequencing:** This technique on a wide scale genome evaluate methylated DNA fragments for gene-specific DNA methylation.
8- **Electrochemical tools:** It is redox reactions-based DNA methylation
9- **Nanoparticle-based technique:** It is detection of DNA methylation which is Methylated CpG region capture-based.
10- **SERS (Surface-enhanced raman scattering) based DNA methylation profiling:** Allows to discriminate benign and malignant DNA.

THE CLINICAL IMPLICATIONS OF DNA METHYLATION

DNA methylation studies play an important role in both diagnosis and prognosis. DNA
methylation is considered a promising biomarker, and its patterns can be detected in different biological samples, including tissue biopsies and body fluids such as blood and urine, especially through the analysis of circulating cell-free DNA (21, 22).

Promoter methylation events have been identified in 168 genes, including BRCA1, using The Cancer Genome Atlas (TCGA) high-grade serous ovarian carcinoma datasets. Notably, BRCA1 inactivation due to promoter methylation and inactivation due to gene mutations are mutually exclusive events. In comparison the patients of high-grade serous cystadenocarcinoma ovary carrying genetic mutations BRCA1 genetic mutations show overall better survival as compared to those having BRCA1 wild-type gene. However ,patients with epigenetic silencing of BRCA1 do not have this advantage in terms of survival(22).

In one study hypermethylation of the UQCRH locus was observed in 36% of the clear cell RCC and was found to be related to higher grade stage disease. In addition clinical outcomes which were corelated with the epigenetic signatures were found to be similar to Warburg effect. One of the drivers of this shift was hypomethylation promoter of MIR21, is one of the reason for this shift and is a negative regulator of the tumor suppressor gene PTEN. This loss of promoter methylation is well correlated with the increased expression of MIR21 and found to be a worse prognostic indicator (23, 24).

In early stages of tumorigenesis,DNA hypermethylation can happen is strongly related to tumor progression, so it serve as a vital indicator of patient's survival (25). Also in addition to this DNA hypomethylation is often seen in early tumorigenesis like even in hyperplasia (25). DNA hypomethylation is generally related more to the stage of the cancer and progression (26). But interestingly it also is dependent on the type of the tumor type and the specimen (26, 27). LINE-1 hypomethylation in prostatic adenocarcinoma is related to regional lymph node metastasis(28). Both juxtacentromeric and centromeric satellite DNA hypomethylation was found to be linked with tumor grade of ovarian epithelial malignancies and these are also proved to be a significant marker for overall survival and the risk of relapse (29). More and more researches have shown this tumor progression link and DNA hypomethylation leading to it. Gene hypomethylation shows an increase in the tumor progression.

DNA METHYLATION AND CANCER THERAPEUTICS

Liang et al. reported DNA methylation-mediated tumorigenesis (30). Further, gave an overview about the development of DNA methylation based epigenetic therapies (Fig 3). Researchers have suggested because of pan-cancer DNA methylation patterns, that by analyzing DNA methylation isoforms and immune molecule epigenetic signatures, it may be possible that in future we will be personalizing an individual patient's therapy options by targeting several DNA methylations, and so the immune proteomics molecular targets.Cancer epigenomic variabilities leads to the substantial differences in distinct subsets of tumor cells(31). Therefore it is vital to identify the key methylation changes in different cancers by using pan-cancer analyses which will lead to the identification of relevant molecular targets.Chimeric antigen receptor (CAR) T-cell therapy is innovative personalized immunotherapy effective against many hematologic tumors. In addition better proliferation, increased anti-tumor activity and enhanced effector functions, exhibiting reduced T cell exhaustion is shown by DNMT3A knockdown in CAR-T cells.

DNMTs in tumor drug resistance have shown a dual role. In therapy with decitabine, an inhibitor molecule of DNMT1, increases the sensitivity to sorafenib by pancreatic carcinoma cells. Further, DNMT3B inhibition with nanaomycin A significantly increases the sorafenib sensitivity of hepatocellular carcinoma (HCC) cells (32).

Increasing focus is given to DNMT inhibitors in cancer therapy as these have significant potential for treating various cancers. Currently researchers are therefore aiming to develop more precise DNMT inhibitors in order to selectively targeting DNA methylation in cancer cells while saving damage to the normal healthy cells. DNMT therapies look promising for different cancer patients in terms of the survival rate and also improve tailored treatment options and better drug delivery systems(33).

TABLE 1. (DNMTs) role in different in cancers.

DNMTs	**Carcinoma type**	**Functions**
DNMT1	Esophageal cancer, pancreatic cancer, Colon cancer,	During DNA replication, maintains methyl group in the DNA semi-methylated stand.
DNMT2	Breast Cancer	Role in cytosine methylation
DNMT3a	Liver cancer, lymphoma, AML	Transports methyl group to the specific CpG DNA side.
DNMT3b	Breast cancer, prostate cancer, AML	Works with H3K36me3 and RNA Pol-II and in de novo and is involved in DNA methylation

Table1. Describes the roles of different DNMTs in DNA methylation DNA methylation.

Table 2: Roles and Functions of m5C modification regulators

Type of Cancer	m5C regulators	Expression	Targeted genes	Molecular functions	Mechanism
HNSC	NSUN2	up	TEAD1	Enhancing tumor cell proliferation and invasion of HNSC	Increased mRNA stability of TEAD1
AML	TET2		TSPAN13	Promotes leukemia development, leukemia stem cell migration/homing, and leukemia stem cell self-renewal	Increases the stability and expression of TSPAN13 transcripts
Hepato Cellular Carcinoma	ALYREF	up	EGFR	Facilitates cell proliferation, invasion, and EMT in HCC	Induces m5C modification and increases the stabilization of EGFR mRNA and pSTAT3 activation.
HCC	NSUN5	up	ZEED3	Promotes proliferation of HCC cells	Activates Wnt/β-catenin signaling pathway
Glioma	NSUN2	up	ATX	Enhances glioma cells proliferation	Enhancing ATX mRNA translation
Gastric carcinoma	NSUN2	up	NTN1	Promotes neural invasion in GC	DIAPH2-AS1 stabilizes NSUN2 and enhances the m5C modification of NTN1
Gastric Carcinoma	NSUN2	up	FOXC2	Promotes proliferation, migration, and invasion of GC cells	FOXC2-AS1 facilitates NSUN2 recruitment to FOXC2 mRNA, enhancing its m5C modification and interaction with YBX1

Lung Carcinoma	ALYREF	up	YAP1	Enhances tumor progression in NSCLC	Interacts with LINC02159; increase the stability of YAP1 mRNA; activates Hippo and beta-catenin
Gastric Carcinoma	NSUN2	up	ERK1/2	Promotes chemosensitivity in GC	Increases ERK1/2 phosphorylation; regulates Bcl-2 and Bax
Glioma	NSUN2	up	ATX	Enhances glioma cells proliferation	Enhancing ATX mRNA translation

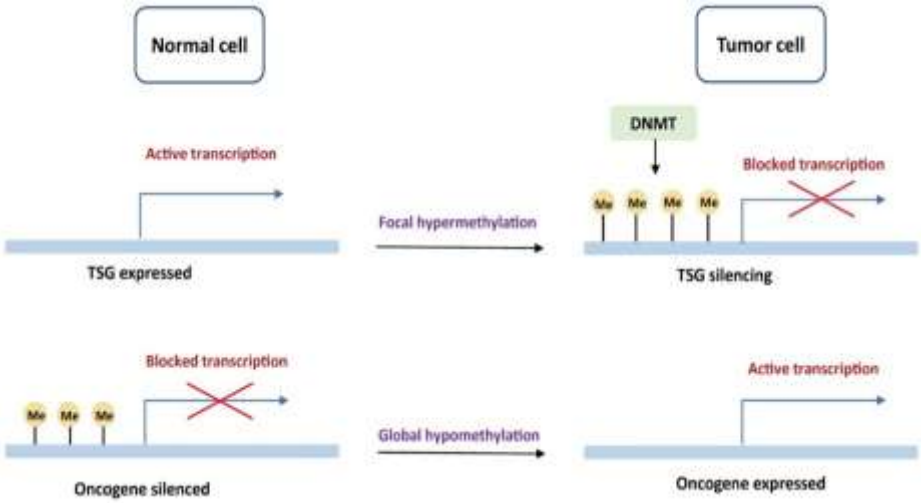

Figure 1: Tumor suppressor genes in normal cells are demethylated and the expressed but on the other hand oncogenes are methylated and unexpressed. Tumor suppressor genes in cancer cells are shut off by DNA de novo methylation with DNMT, while because of global hypomethylation oncogenes are transcribed actively.

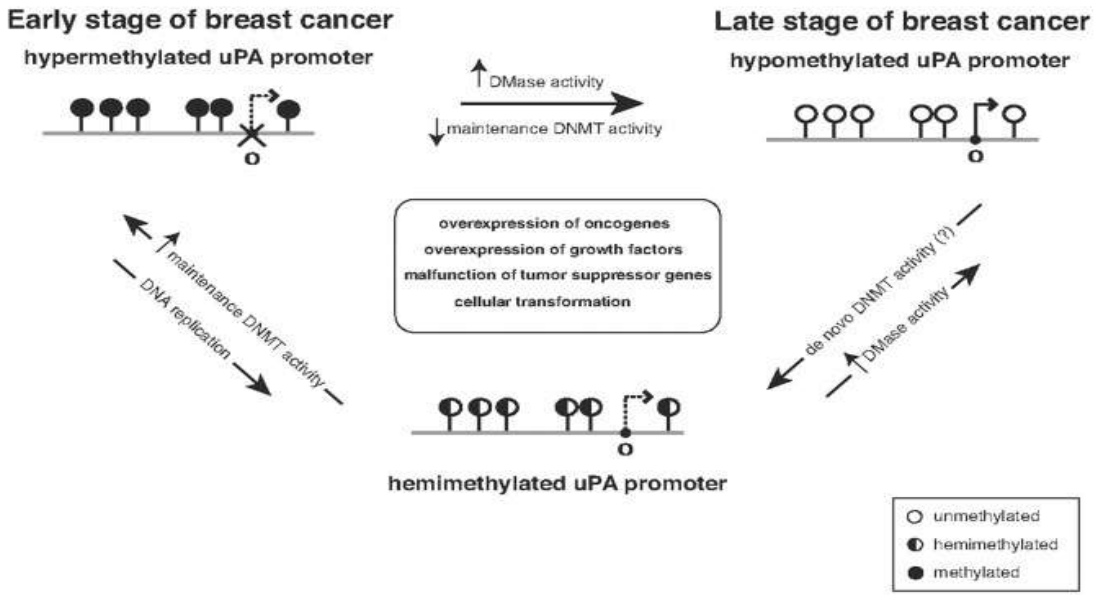

Figure 2: This diagram shows abnormal DNA methylation patterns by integrative multiomic carcinoma profiling which promote cancer and shows their links immunotherapy. UCEC Uterine corpus endometrial carcinoma, GBM

glioblastoma multiforme, LUAD Lung adenocarcinoma, HNSCC, head and neck squamous cell carcinoma, PDAC, LSCC Lung squamous cell carcinoma, Pancreatic adenocarcinoma, ccRCC, clear cell renal cell carcinoma

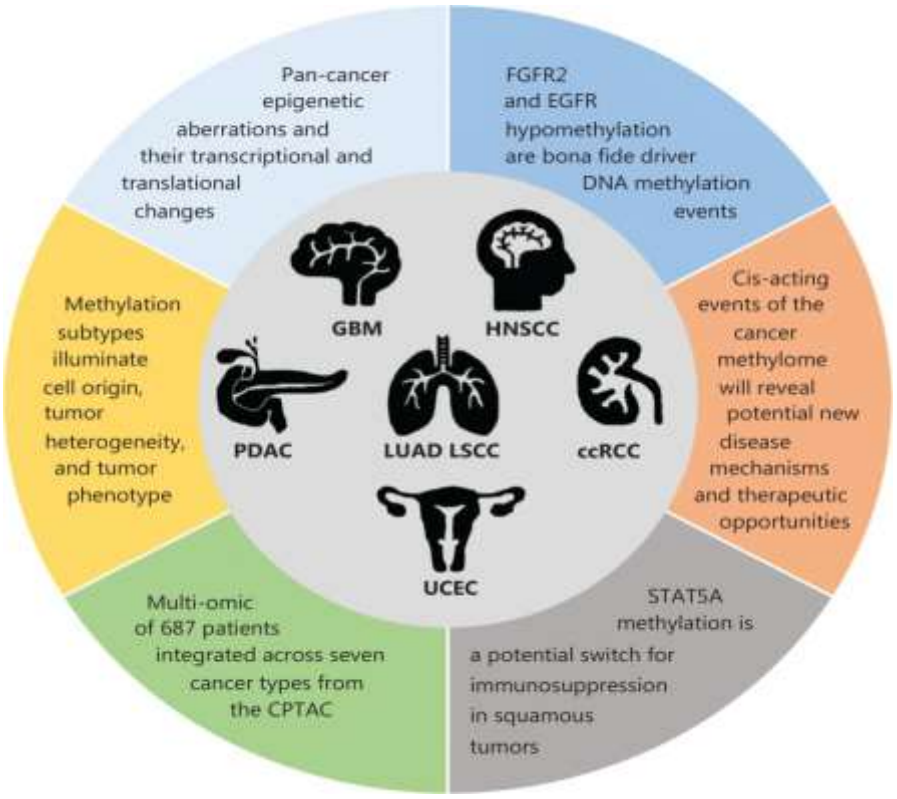

Figure 3: This diagram shows abnormal DNA methylation patterns by integrative multiomic carcinoma profiling which promote cancer and shows their links immunotherapy. UCEC Uterine corpus endometrial carcinoma, GBM glioblastoma multiforme, LUAD Lung adenocarcinoma, HNSCC, head and neck squamous cell carcinoma, PDAC, LSCC Lung squamous cell carcinoma, Pancreatic adenocarcinoma, ccRCC, clear cell renal cell carcinoma

CONCLUSIONS

DNA methylation plays an important role in how cancer starts and grows by controlling how genes work and keeping cells stable. Changes in DNA methylation can be useful as markers to help diagnose cancer, predict outcomes, and guide treatment. However, it is still difficult to fully understand these changes and to clearly separate cancer-related signals from normal cells. Future research that combines methylation studies with other molecular methods may help in early detection, better risk assessment, and more personalized cancer treatment.

Conflict of Interest Statement
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