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# The Role of Methylation in Oncogene Regulation

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## ABSTRACT

DNA methylation in cancer plays a pleotropic of roles, helping to change the normal regulation of gene expression to a disease pattern. There are two types of common changes in DNA methylation that appear in a tumour cell of the same tissue type having normal cell also and demethylation within many regions of the genome in coordination with de novo methylation of selected CpG islands. The stable nature of DNA as compared to RNA and the availability of high-throughput techniques for evaluation of DNA methylation in large sample sets add good advantages for its clinical applications. The present systematic review explains the aberrant methylation and the integration proteomics, highlight the mechanisms leading to different methylation subgroups in DNA profiling of tumour genomes.

**Keywords**: Cancer, DNA, Methylation, Genome, Proteomics

## INTRODUCTION

"Molecular characterizations of large cohorts of cancer individuals using tomour samples from all important organs have made available a wealth of genomic, transcriptomic, epigenomic and proteomic data, enabling integrated analysis across different tomour types as called pan-cancer analyses" [1]. Currently, mutational landscapes are emerging as novel oncogenic signatures and cancer driver mutations. These mini reviews aim to identify and explain the genomic and epigenomic similarities, differences among distinct cancer types and independent of their tissue of origin. Epigenetic modification is now being taken as additional layers in the regulation of gene expression. DNA methylation is a marker as characterized epigenetic modification and is involved in the modulation of gene expression, genome stability and developmental processes [2]. High-throughput methods, including array and sequencing-based technologies provide genome-scale DNA methylation maps, called methylomes have confirmed abnormal methylation as a hallmark in all cancer types and are used to detect novel methylation-based cancer biomarkers [3].

DNA methylation in cancer plays a diverse role, helping to change the normal regulation of gene expression to a disease pattern. There are two types of general changes in DNA methylation that appear to occur in a tomour as compared with normal cells of the same tissue type: demethylation within many regions of the genome in coordination with de novo methylation of select CpG islands [3]. Epigenetic factors change during development, and formation of different tissues including histone modifications, CpG island methylations and chromatin reorganizations which in turn regulate activation of particular genes. Despite early observations suggesting that modification on a wide range of CpG islands occurs mainly at promoters of tomour suppressor genes in growth [4]. There are over 13,000 constitutively unmethylated CpG islands in the human genome, approximately 2,000 of these are marked with polycomb, a protein complex that operates as a repressor by bringing about local heterochromatinization. In the tomour this complex appears to be responsible for recruiting the de novo methylases, DNMT3A (DNA methyltransferase 3 alpha), and 3 beta that probably bring about the abnormal modification seen at these sites [5].

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In 2012, the Cancer Genome Atlas (TCGA) Pan-Cancer project was launched with the aim of collecting, analyzing and interpreting data across different tumour types and of making these resources publically available. Multidisciplinary international consortia like TCGA or ICGC (International Cancer Genome Consortium) have produced methylomes for thousands of cancer samples. Integrative data analyses have decrypted that methylomes in subgroups within one tumour type might differ more than between distinct cancer types [6]. Even within the similar tumour, regional diversity in DNA methylation alterations have been recognized, associated with intrinsic tumour heterogeneity [7]. A remarkable initial reporting was that tomour samples cluster largely in order to their tissue of origin. Analyses of various tumour entities explained that gastric, colorectal and endometrial cancers have similar highly methylated subgroups which associated with tomours with microsatellite instability and hyper-methylation of the MLH1 (MutL homolog 1) promoter [8]. Subtypes of serous endometrial, breast, high-grade serous ovarian, gastric and colorectal carcinomas are associated with high chromosomal instability as well as with recurrent TP53 (tumour protein p53) mutations and share patterns of lower methylation. However, emerging evidence explains that cancer genomes show frequent mutations in epigenetic regulators, evidencing a close interplay between genomic and epigenomic events [9]. Deciphering the mechanisms underlying methylation patterns will facilitate the identification of novel therapeutic targets [1].

## METHYLATION AND TOMOURIGENESIS

Considering new data in the field of DNA methylation, it is now possible to propose a model for how this modification can influence to mourigenesis. The findings on DNA methylation in cancer can be interpreted in two different ways. On the one hand, it is possible that normal cells become transformed through the occurrence of driver mutations and then undergo de novo and demethylation as a result of this event, setting in motion a series of programmed changes in gene expression [10]. Alternatively, a subpopulation of normal cells that have already undergone changes in methylation, perhaps as a result of aging, may represent preferred targets for oncogenic transformation. According to this, the presence of abnormal methylation in cancer actually comes about through selection of pre-existing normal cells characterized by a methylator phenotype. Once this is formed, it would, of course, be preserved in progeny cells, much in the same manner as mutations [11] **(Figure 1)**.

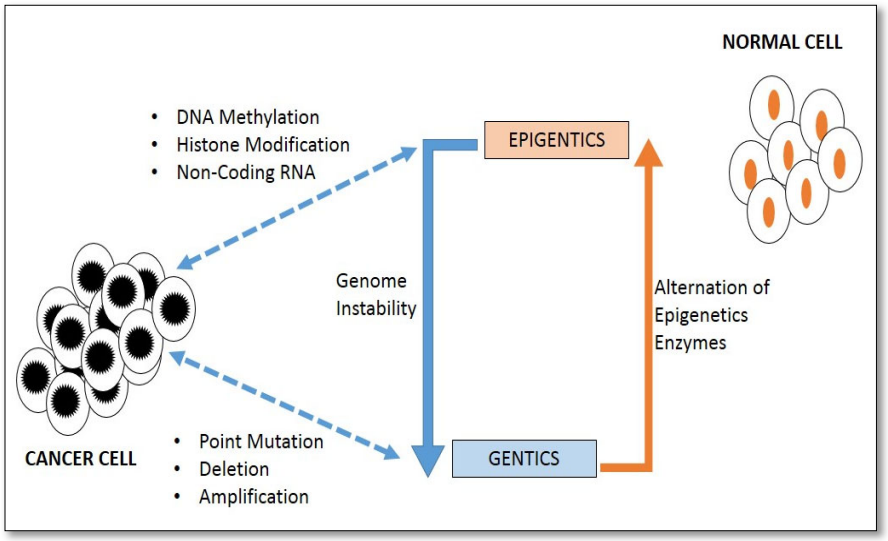


**Figure 1.** Role of methylation in cancer.

SIRT1 as an oncogene is that it supports the survival of cancer stem cells (CSCs). The regulation of caloric restriction through food intake reported to regulate the progressive ageing disorder via suppression of the anti-aging gene Sirt 1. Sirtuin 1 regulation has been also reported to link with cancer [12]. Islam et al. [13] reported that SIRT1 hypermethylation is associated with malignant transformation and it could be a good marker. Reactivation of cancer-causing gene has been reported during inhibition of SIRT1 [14].

## CONCLUSION

Methylation of DNA was the first epigenetic modification to be recognized in cancer. It is considered to be a marker of cancer. It is detected in several types of cancer cells including colon, breast, ovarian and cervical cancer cells. The comparison of DNA methylation patterns across cancer types (pan-cancer methylome analyses) has revealed distinct subgroups of tomours that share similar methylation patterns. Knowledge gained from pan-cancer methylome

analyses will aid the development of diagnostic and prognostic biomarkers, improve patient stratification and the discovery of novel druggable targets for therapy, and will generate hypotheses for innovative clinical trial designs based on methylation subgroups rather than on cancer subtypes.

The genome-wide methylation profiles generated by TCGA and others has shown that aberrant methylomes are hallmarks of cancer and are useful in classifying tomour subgroups as well as for identifying novel clinical biomarkers. The identification of a wide number of genes that are affected by aberrant DNA methylation in cancer has highlighted the potential use of this epigenetic modification as a biomarker for cancer risk diagnosis, prognosis and prediction of therapy response. The stable nature of DNA compared with RNA and the availability of high-throughput techniques for measurement of DNA methylation in large sample sets add advantages for its clinical application.

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