

The role of DNA methylation in carcinogenesis

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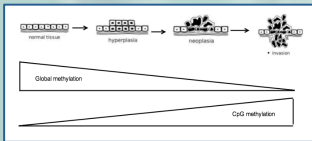
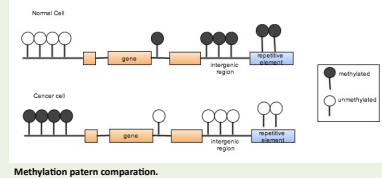


INTRODUCTION.

Epigenetics is the study of the group of heritable modifications that do not change the sequence of the bases of the DNA but change DNA conformation and as a consequence the expression of genes. Epigenetic mechanisms regulate important biological processes like the ones responsible of cellular division and differentiation involved in disease like cancer so the disruption of the epigenome contributes to cancer development. Although there are many epigenetic mechanisms altered in cancer, the best-studied one is the aberrant methylation of DNA.

DNA METHYLATION AND CANCER.

Cancer cells show a different methylation pattern compared to normal cells. The hypermethylation of CpG islands often causes the transcriptional inactivation of tumour suppressor genes directly driving the carcinogenic process.



Clinical utility.

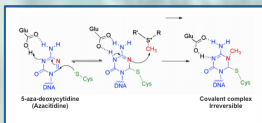
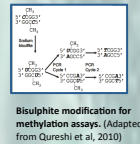
Transformed cells with specific hypermethylation patterns on certain genes are reliable biomarkers for particular types and stages of cancer. They are clinically useful for tumour detection, outcome prediction, treatment selection and monitoring.

DNA methylation detection methods.

DNA methylation can be found in several types of biological fluids so it can be obtained noninvasively and analysed. The majority of methods for methylation analysis begin with the bisulphite conversion that creates different sequences in methylated and unmethylated fragments that can be detected by a variety of techniques.

Detection method	Amount of DNA required	Throughput	Cost
Enzymatic (HpaII/SfiI)	Large	Low	Moderate
Methylase sensitive PCR	Low	Low	Low
COBRA	Low	Low	Low
Methylkit	Low	Medium	Low
DNA methylation microarray	Low	Medium	High

Methods to detect DNA methylation and comparison of their features. (Adapted from Qureshi et al., 2010)



Epigenetic therapy.

In contrast to genetic alterations, gene silencing by epigenetic modifications is potentially reversible and there have been developed several drugs against different types of epigenetic processes. DNA methyltransferase inhibitors (DNMTi) are the best known of these drugs. Two of them (azacitidine and decitabine) have been approved by the Food and Drug Administration (FDA). When these compounds get to the DNA, they form a covalent irreversible complex with DNMTs trapping them.

EXAMPLE OF EPIGENETIC THERAPY.

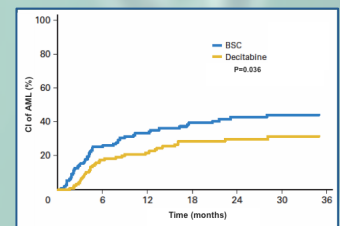
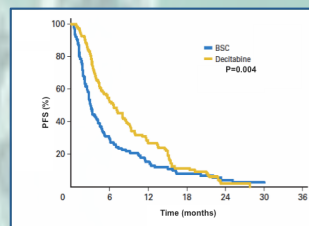
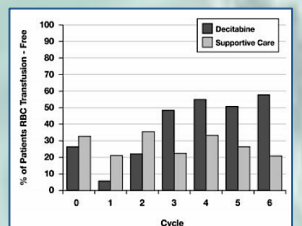
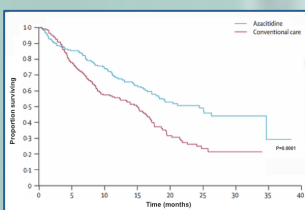
It was found that a notable proportion of the mutated genes in Myelodysplastic Syndrome (MDS) affect genes involved in epigenetic maintenance. The most well-studied alteration is the aberrant DNA methylation. Epigenetically active drugs azacitidine and decitabine have been approved for treatment of this type of cancer introducing a new option of treatment that was limited before to toxic traditional induction chemotherapeutics.

Azacitidine results.

- Improves overall survival (OS)
- Delays the transformation to AML in high-grade MDS patients
- Produces significant responses in patients with low blast count AML

Decitabine results.

- Produces red blood cell transfusion-independence
- Produces elongation of progression-free survival
- Improves global health status by improving fatigue and physical functioning.



CONCLUSIONS.

Epigenetic changes are associated with cancer development but are also progressive and reversible and these makes them a potential target for the therapeutic intervention and development of tumour prevention strategies. Aberrant methylation is the most studied epigenome alteration seen in cancer. The purpose of epigenetic therapy is to reverse the epigenetic alterations in cancers cells and restore the "normal epigenome". Of all the DNMTi discovered, azacitidine and decitabine have already demonstrated the utility of the epigenetic therapy that opens a possibility of stopping some types of cancer development but there is still a lot of work to do finding specific alterations for each cancer and the right drugs and doses for treatment.

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