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DNA methylation introduction

DNA methylation is an epigenetic mechanism known to affect gene expression.

DNA methylation (5 mC) is formed by the addition of a methyl group to the 5' position of cytosine residues within a CpG dinucleotide context in mammals.

The majority of CpG sites are highly methylated in the mammalian genome with the exception of CpG islands which are largely unmethylated.

Genome-wide demethylation happens in the early stages of embryogenesis to form totipotent cells. This is followed by *de novo* methylation where tissue-specific genes undergo demethylation in their cell type of expression.[1]

DNA methylation is maintained during DNA replication of somatic cells.[2] When the literature refers to DNA methylation as heritable it generally refers to heritability across cell divisions, not transgenerational.

Some regions of the methylome vary across different tissue or cell types.[3]

DNA methylation and disease

Alterations in DNA methylation are associated with numerous diseases, including cancer, cardiovascular diseases, metabolic disorders, and neurodegenerative diseases such as those caused by expansion of microsatellite repeat elements.[4]

Therefore, identifying therapeutics that inhibit these epigenetic changes are of great interest.

Cancer

Aberrant DNA methylation has been implicated as one of the mechanisms driving tumour onset, development, progression and recurrence.

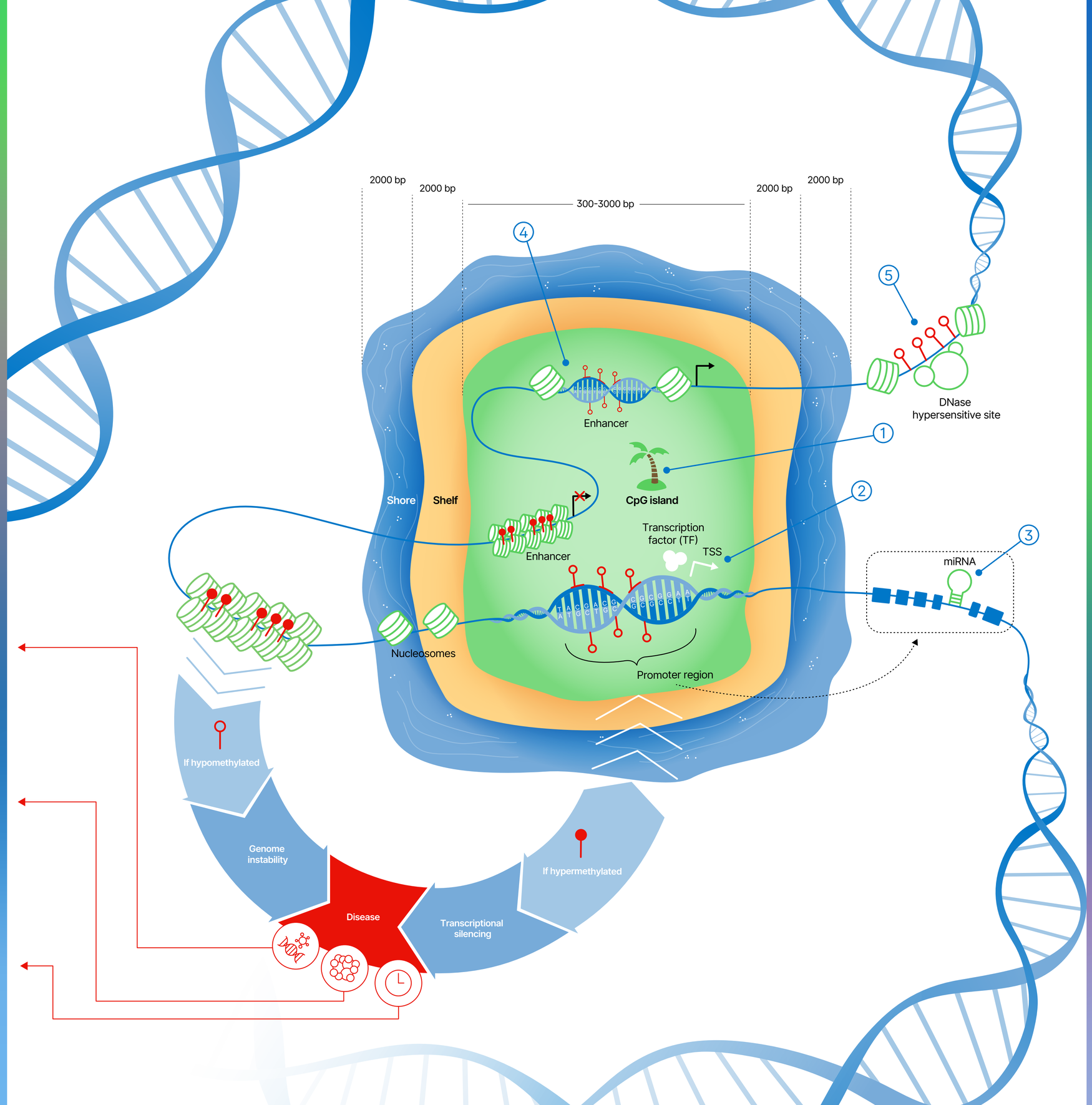
Epigenetic gene silencing due to promoter CpG island hypermethylation is one of the most common mechanisms by which tumour suppressor genes are inactivated during tumourigenesis.

Another typical feature of methylation in carcinogenesis is global DNA hypomethylation linked to genomic instability.[5]

Aging and the Epigenetic Clock

Changes in DNA methylation correlate with age and it has been shown that a set of differentially methylated loci can be used to calculate the biological age of mammals, with potential predictive powers for life expectancy. This has been dubbed the "Epigenetic Clock".[6]

This discovery has led to research into the potential to delay or reverse these epigenetic changes with life style changes, dietary interventions, pharmaceutical approaches, or cellular reprogramming.



The relationship between DNA methylation and specific elements of the mammalian genome

1 CpG islands

CpG islands (or CG islands) are regions in the genome with a high frequency of CpG sites, usually 300–3,000 base pairs long. CpG islands are mainly located in promoter regions and found in almost half of all human genes.

2 Promoter regions

Promoter regions are DNA sequences that define where transcription of a gene by RNA polymerase begins. Promoters are typically located directly upstream or at the 5' end of the transcription start site (TSS). Promoter regions are 100–1,000 base pairs long. RNA polymerase and the necessary transcription factors (TFs) bind to the promoter sequence and initiate transcription.

3 miRNA promoter regions

DNA methylation of promoter regions of miRNA genes can modulate their transcription levels and hypermethylation appears to contribute to miRNA dysregulation in cancer.

4 Enhancers

Enhancers are short (20–400 bp) DNA sequences that bind tissue-specific transcription factors and can regulate transcription at distant loci through chromosome looping[7]. Most are found in intergenic regions, but some are also found within genes[8].

5 DNase hypersensitivity sites

DNase hypersensitivity sites (DHSs) are short nucleotide regions of the genome that are extremely sensitive to cleavage by the DNase I enzyme and various other nucleases. In these regions, the nucleosomal structure is less condensed, making the DNA more accessible to binding by proteins like transcription factors and DNase I.

Methylated CpG falling within DHSs impedes the association of transcription factor to DNA, inhibiting the accessibility of chromatin.[9]

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