# Epigenetics Control of Gene Expression | Cancer Epigenetics | Capstone Final Project | The University of Melbourne

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## *What alterations are made to DNA methylation in cancer?*

Overall, DNA methylation in cancer undergoes locus-specific hy*per*methylation and genome-wide hy*po*methylation.

In normal genomes, DNA methylation at CpG islands serves to provide genomic stability, cause transcriptional silencing, or allow for genomic imprinting. However, in cancer, CpG islands are hypermethylated, leading to the transcriptional silencing of critical tumor suppressor genes. Additionally, regions adjacent to the CpG islands (CpG island shores) may also be hypermethylated, a phenomenon well exhibited by *GSTP1* hypermethylation in prostate cancers.

The disruption of methylation at CpG islands can contribute to cancer in several ways. Transcriptional silencing of tumor suppressor genes or activation of oncogenes, both caused by localized hypermethylation and genome-wide hypomethylation, can lead to uncontrolled cell proliferation, a hallmark of cancer. Additionally, disruptions to DNA methylation at CpG islands can interfere with its ability to provide genomic stability; the resulting genomic instability is a trademark of cancer.

In normal genomes, DNA methylation at intergenic regions and repetitive elements generally serves to uphold genomic integrity and to prevent transposition, transcriptional interference, or illegitimate recombinations. However, in cancer, hypomethylation of intergenic regions/repetitive elements increases genomic instability, leading to possible deletions, reciprocal translocations, or additions that cause abnormalities in the karyotype. These resulting increases in mutagenesis are characteristic of cancer.

## *What alterations are made to imprinting in cancer, and how does the H19/IGF2 cluster display these disruptions?*

Let's start by analyzing the normal methylation pattern of *H19*/*IGF2* on the maternal and paternal alleles. On the maternal allele, the imprint control region (ICR) is unmethylated, allowing for the binding of the CTCF protein. This prevents *IGF2* promoters from binding and thus transcriptionally silences *IGF2*. However, on the paternal allele, methylation is required during spermatogenesis. This prevents the binding of the CTCF protein, leading to the binding of *IGF2* promoters and the expression of the *IGF2* gene.

In Wilm's tumor, imprinting is lost due to the hypermethylation of the ICR. Because this methylation on the maternal allele prevents the CTCF protein from binding, the result is the biallelic expression of *IGF2* in Wilm's tumor.

These disruptions to the *H19*/*IGF2* cluster can contribute to cancer in several ways. Normally, imprinting in the cluster ensures that *IGF2* is only expressed from the paternal allele. However, when this imprinting is disrupted, allele-specific regulation is lost, leading to enhanced cell proliferation and promoted tumorigenesis. Another consequence of this disruption is the transcriptional silencing of *H19*, a tumor suppressor. This silencing similarly results in cell proliferation and tumorigenesis.

***The Economist article "Cancer's Epicenter" describes several drugs that affect epigenetic processes. Explain how Decitabine may be used to treat cancer, with reference to effects on the epigenome.***

Decitabine belongs to a class of epigenetic inhibitors known as DNA methyltransferase inhibitors (DNMTi). As a DNMTi, Decitabine prevents DNA methyltransferase enzymes from hypermethylating CpG islands, which could lead to cancer as previously mentioned. In fact, Decitabine can reverse the effects of hypermethylation on CpG islands by demethylation, allowing for the expression of tumor suppressor and other regulatory genes. By both preventing hypermethylation and demethylating pre-existing hypermethylation at CpG islands, Decitabine activates tumor suppressor genes that can inhibit the development and metastasis of cancer.

Through demethylation, Decitabine may also reactivate cell differentiation, which is sometimes lost due to disruptions in methylation patterns caused by cancer. Since the loss of cell differentiation is a hallmark of cancer, by restoring it, Decitabine effectively inhibits cancer growth.

***In the previously mentioned Economist article, Dr. Stephen Baylin speculates that "epigenetic drugs altered the tumor cells in some lasting way that made them more susceptible to standard chemotherapy." How can drugs that alter DNA methylation have effects that last beyond the period of drug treatment? Discuss whether there are any periods of development in which to avoid treating patients with such drugs.***

DNA methylation can have enduring lifetime or even transgenerational effects. Alterations to DNA methylation made in early development will remain relatively stable and unchanged throughout the organism's lifetime. On a cellular level, there also exists a sort of epigenetic "memory," where modified epigenetic marks can persist through multiple cell divisions or developmental stages. On a larger scale, environmental changes that disrupt DNA methylation may have transgenerational effects, where epigenetic modifications can transfer from parent to offspring.

Many of these permanent changes will occur if the epigenetic alterations are made during *sensitive periods*. Sensitive periods are essentially windows of time, such as during germ cell development or early embryonic development, where the epigenome is reprogrammed and is more susceptible to modifying external factors, including changes in nutrition, increases/decreases in stress, or the introduction of toxins.

Treatment should be avoided during these sensitive periods. Induced epigenetic changes made during these timeframes may disrupt normal development, as natural epigenetic programming is necessary for growth, cellular identity, and function. Additionally, due to the enduring effect of epigenetic changes made during sensitive periods, the treatment may modify epigenetic marks more permanently than is expected or advised, and these impacts can span multiple generations.

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