Microreviews in Cell and Molecular Biology

2012

Epigenetics, DNA Methylation, and Their Role in Cancer

Author: Nick Jordan
Major: Physiology/Psychology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

Key Words:
Epigenetics, DNA Methylation, Cancer

"Epigenetics" refers to study changes of gene expression that do not affect changes in the nucleotide sequence. One mechanism of epigenetic modification is DNA methylation. DNA methylation is an important process of normal development in organisms. Specifically, it is an integral part of cell differentiation, and is thus different between different species, organs, and tissues. DNA methylation involves the addition of a methyl group to DNA (Vanyushin, B.F., Mazin, A.L., Vasiliev, V.K., and Beloz- ersky, A.N., 1973). The methyl group is added to cytosine (or sometimes adenine) bases. With the addition of a methyl group, cytosine is converted to 5-methylcytosine and adenine is converted to N6-methyladenine. DNA methylation occurs often in repeated DNA sequences. DNA methylation can modify the structure, and thus the function, of proteins in the body (Vanyushin, B.F., 1973). The modifications can affect all processes in the cells. Hypermethylation often leads to suppressed expression. It has been shown that malignant cells have irregular patterns of DNA methylation; therefore, disruption in these patterns has been used to diagnose carcinogenesis (Shif, M., 2005). DNA methylation is now being intensely studied due to its potential role in tumorigenesis (Kulis, M., Esteller, M, 2010). Also, although epigenetic changes do not affect the DNA sequence of an organism, recent research has shown that these alterations persist through cell divisions and may be heritable and passed down to offspring.

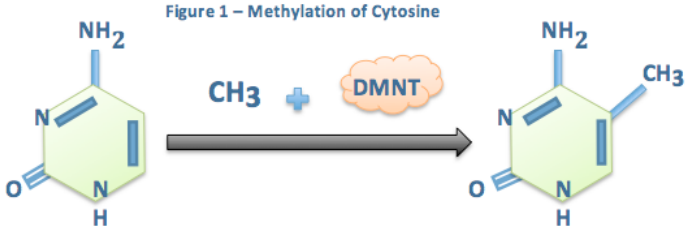
Introduction

Epigenetic changes are necessary for properly controlling gene expression. These changes are heritable, and occur independently of DNA nucleotide sequence changes.

The study of epigenetics may explain how a zygote may transform to somatic tissue, though the DNA sequence is stagnant. It also may explain how an individual may contract a particular genetic disease, without his or her identical twin having the same disease. DNA methylation is one such mechanism of epigenetic change. A disruption of DNA methylation can lead to the malfunctioning of cell processes and even cancer (Kulis, M., Esteller, M., 2010). DNA methylation is the addition of a methyl group to a cytosine, to become 5-methylcytosine (CpG) (Bird A.P., 1986).

As a whole, an organism's genome is weakly methylated. CpG content is usually found in clusters called CpG islands (Bird A.P., 1986). These are abbreviated as CGIs. CGIs are present mostly in promotor regions; in fact, research has shown that almost 60% of promotors are CpG enriched (Bird A.P., 1986). Methylation is regulated by DNA methyltransferase enzymes, or DNMTs. 5 of these enzymes have been found in mammals, but only three have been shown to be involved in the catalyzation of methylation. The three DNMTs involved in the catalyzation are DNMT1, DNMT3a, and DNMT3b. These three enzymes are known as "de novo enzymes". The use of a DMNT to methylate cytosine is shown below in Figure 1.

Figure 1 – Methylation of Cytosine



Recent Progress

As stated before, DNA methylation is necessary for normal development of an organism. Disruptions in this pattern can thus lead to improper cell functioning. Recent studies have found that hypo/hyper-methylation can potentially lead to carcinogenesis. Often, an unhealthy decrease in content leads to the activation of normally suppressed genes. Hyper methylation, especially in tumor suppressing genes, can also lead to the proliferation of cancer cells (Kulis, M., Esteller, M., 2010).

As previously stated, methylation can be reversible. It should also be stated, however, that CpG content can also undergo a separate conversion to 5-hydroxymethylcytosin (Bird A.P., 1986). This change is very similar to the unmodified 5-methylcytosine. The impact of this conversion is not yet understood, and is a future topic of study. It is known that methylation has an effect on how the DNA binds with different proteins, but it is still unclear how the inhibition of gene expression can be caused by DNA methylation (Vanyushin, B.F., 1973). One recent hypothesis is that DNA may create a promotor binding barrier for some transcription factors. Another proposition is that methyl-CpG binding proteins associate with enzymes that compress the chromatin to silence the gene (Bird A., Wolffe A.P., 1999)

Apart from the enzymes, the specificity of methylation is also due to the structure of the chromatin, and how accessible the binding sites are (Bird A., Wolffe A.P, 1999). Ultimately, methylation is regulated by hormones. The environment can have an affect on hormones released in an organism's body; for this reason, DNA methylation is regulated in part by the environment. For example, phytohormones repress the CpG content of DNA strands in plants. Another example is how the antioxidant BHT increases methyltransferase activity to increase CpG content. This positively affects the expression of the S-adenosylmethionine-synthetase and p53 genes (Bird A.P., 1986).

Semimethylation of DNA at different stages of cell division has been shown. After the replication is complete, the enzyme DMNT1 completes the methylation of the semimethylated sites. Thus, this epigenetic change to gene expression is inherited. Some of these changes are favorable, but inherited methylation can also lead to disease.

Discussion

The research in DNA methylation is promising, but there is much more to learn about the process. For example, the structure of chromatin must be more thoroughly researched to understand the specificity of DNA methytransferase binding (Bird A., Wolffe A.P. 1999). If methylation becomes better understood, the possibility of DNA methylation markers can become a valuable tool. It is also interesting that there has been so much evidence to suggest the correlation between hypo/hyper-methylation with cancer (Kulis, M., Esteller, M., 2010). If these markers are in place, clinicians may be able to determine predispositions to cancer and other diseases (Shif, M., 2005). Also, since methylation is reversible, it is reasonable to think that the carcinogenic methylation of DNA sequencing may someday be able to be reversed to a healthy expression.

References

Bird A., Wolffe A.P. (1999) Methylation-induced repression—Belts, braces and chromatin. Cell **99**:451–454.

Bird A.P., (1986) CpG-rich islands and the function of DNA methylation. Nature**321**:209–213

Marta Kulis, Manel Esteller, 2 - DNA Methylation and Cancer, In: Zdenko Herceg and Toshikazu Ushijima, Editor(s), Advances in Genetics, Academic Press, 2010, Volume 70, Pages 27-56, ISSN 0065-2660, ISBN 9780123808660, 10.1016/B978-0-12-380866-0.60002-2. (http://www.sciencedirect.com/science/article/pii/B9780123808660600022

Shif, M., DNA Methylation and Demethylation as Tar- gets for Anticancer Therapy, *Biokhimiya*, 2005, vol. 70, pp. 651–669.

Vanyushin, B.F., Mazin, A.L., Vasiliev, V.K., and Beloz- ersky, A.N., The Content of 5-Methylcytosine in Ani- mal DNA: the Species and Tissue Specificity, *Biochim. Biophys. Acta*, 1973, vol. 299, pp. 3974–03.

