DOCUMENT SUMMARY

This foundational 2003 review by Rudolf Jaenisch and Adrian Bird explains how **epigenetic** mechanisms, primarily **DNA methylation** and **histone modifications**, allow the genome to integrate signals from both internal development and the external environment. The paper details how these processes establish and maintain stable patterns of gene expression, which are crucial for development, but can also be altered by factors like aging and diet, contributing to diseases like cancer. It provides a comprehensive overview of the molecular machinery, such as DNA methyltransferases (DNMTs) and methyl-CpG binding proteins, that translates these epigenetic marks into biological function.

FILENAME

`jaenisch_2003_research_report_epigenetics_gene_expression`

METADATA

Category: RESEARCH **Type:** report **Relevance:** Core **Update Frequency:** Static **Tags:** #epigenetics #dna-methylation #histone-modification #gene-expression #chromatin #dnmt #environmental-signals #cancer-epigenetics **Related Docs:**

- cheung_2000_research_report_histone_modification_epigenetics
- murray_2005_research_report_monotropism_autism_attention
- brand_guide_communication_neurodiversity_revolution_ai **Supersedes:** N/A

FORMATTED CONTENT

Epigenetic Regulation of Gene Expression: How the Genome Integrates Intrinsic and Environmental Signals

Abstract

Cells of a multicellular organism are genetically homogeneous but structurally and functionally heterogeneous owing to the differential expression of genes. Many of these differences in gene expression arise during development and are subsequently retained through mitosis. Stable alterations of this kind are said to be **'epigenetic'**, because they are heritable in the short term but do not involve mutations of the DNA itself. Research over the past few years has focused on two molecular mechanisms that mediate epigenetic phenomena: **DNA methylation** and

histone modifications. Here, we review advances in the understanding of the mechanism and role of DNA methylation in biological processes. Epigenetic effects by means of DNA methylation have an important role in development but can also arise stochastically as animals age. Identification of proteins that mediate these effects has provided insight into this complex process and diseases that occur when it is perturbed. External influences on epigenetic processes are seen in the effects of diet on long-term diseases such as cancer. Thus, epigenetic mechanisms seem to allow an organism to respond to the environment through changes in gene expression.

Introduction

The term **'epigenetics'**, which literally means 'outside conventional genetics', is now used to describe the study of stable alterations in gene expression potential that arise during development and cell proliferation. Epigenetic processes are essential for development and differentiation, but they can also arise in mature humans and mice, either by random change or under the influence of the environment.

Our rapidly growing understanding of epigenetic processes identifies postsynthetic modification of either the DNA itself or of proteins that intimately associate with DNA as the key mediators. It was proposed in 1975 that **DNA methylation** might be responsible for the stable maintenance of a particular gene expression pattern through mitotic cell division. Since then, ample evidence has been obtained to support this concept, and DNA methylation is now recognized to be a chief contributor to the stability of gene expression states.

Establishing and Maintaining Patterns of DNA Methylation

DNA methylation in mammals is a post-replication modification that is predominantly found in cytosines of the dinucleotide sequence CpG. The extent of DNA methylation changes in an orchestrated way during mammalian development, starting with a wave of demethylation during cleavage, followed by genome-wide de novo methylation after implantation.

Mechanistic insights have come from phenotypic analyses of mice with mutations in the various **DNA methyltransferase (DNMT)** genes.

- **Dnmt1** acts as a **maintenance methyltransferase**, responsible for copying existing methylation patterns to new DNA strands after replication. Deletion of *Dnmt1* results in global demethylation and embryonic lethality.
- **Dnmt3a** and **Dnmt3b** are responsible for global **de novo methylation** (creating new methylation patterns) after implantation.
- **Dnmt3L**, a protein with no intrinsic DNMT activity, cooperates with Dnmt3a and Dnmt3b and is essential for establishing methylation imprints in the female germ line.

Genetic analysis of the various DNMTs has established that DNA methylation is essential for vertebrate development. Loss of methylation causes apoptosis in embryos and fibroblasts and leads to both widespread derepression of ectopic gene expression and transcriptional activation of transposable elements.

In cancer cells, methylation of **CpG islands** (short sequence domains that normally remain unmethylated) is known to contribute to gene silencing. Evidence suggests that a silent chromatin state (e.g., created by histone modifications) can provoke DNA methylation, supporting the view that DNA methylation acts as a system of cellular memory that senses and propagates the silent state.

> Biochemical evidence indicates that DNA methylation is just one component of a wider epigenetic program that includes other postsynthesis modifications of chromatin. Several chromatin modification states are either mutually reinforcing or mutually inhibitory. The resulting feedback loops may function to ensure functional polarization of chromatin domains, stably committing them to either transcriptional activity or transcriptional silence.

Interpreting the DNA Methylation Signal

CTCF and Chromatin Boundaries

One way DNA methylation can repress transcription is by excluding proteins from their DNA binding sites. An example is the chromatin boundary element binding protein, **CTCF**. CpG methylation blocks the binding of CTCF to DNA, which is a critical mechanism in the imprinting of the *Igf2* gene.

The Methyl-CpG Binding Proteins

While repulsive to some proteins, DNA methylation is attractive to others. Progress in understanding methylation-mediated repression came with the characterization of **MeCP2** and its relatives, the **methyl-CpG binding domain proteins (MBDs)**. These proteins specifically target methylated CpG sites.

- A breakthrough was the finding that **MeCP2** interacts with a co-repressor complex containing **histone deacetylases (HDACs)**.
- **MBD2** also associates with HDACs, extending the relationship between histone modification and DNA methylation.

Loss of MBD2 affects gene expression, but the consequences are less severe than the loss of DNMTs, possibly due to redundancy among the methyl-CpG binding proteins.

MeCP2 and Rett Syndrome

Mutations in the X-linked **MECP2** gene are responsible for at least 80% of all cases of **Rett syndrome (RTT)**, an extreme neurological disorder. Most missense mutations are concentrated in the methyl-CpG binding domain, suggesting that binding to methylated DNA is an essential attribute of functional MeCP2. Mouse models with null mutations in *Mecp2* show phenotypic similarities to the human condition, emphasizing the neurological basis of RTT. An obvious hypothesis is that RTT symptoms are due to a failure of effective silencing of methylated genes, but microarray analysis has detected few gene expression differences, suggesting the mechanism may be more subtle.

Epigenetic Regulation and Dysregulation

Genomic Imprinting and X-Chromosome Inactivation

The hallmark of both **X-chromosome inactivation** and **genomic imprinting** is monoallelic gene expression. The maintenance of both processes depends strictly on the continuous activity of **Dnmt1**. To reset imprinting, methylation imprints are removed during primordial germ-cell development and re-established in an allele-specific manner during oogenesis and spermatogenesis, a process dependent on **Dnmt3L**.

Nuclear Cloning and Epigenetic Reprogramming

The cloning of mammals by nuclear transfer is inherently inefficient, likely due to epigenetic abnormalities from faulty reprogramming of the genome. For cloned embryos to develop successfully, the epigenetic program must be reset in the brief period between nuclear transfer and cleavage. Failure to faithfully reprogram "embryonic" genes seems to cause early death. The widespread dysregulation of genes in clones that survive suggests that mammalian development can tolerate a substantial degree of epigenetic abnormality.

Epigenetics and Cancer

Multiple changes in cancer cells are caused by both genetic and epigenetic abnormalities. During carcinogenesis, the genome simultaneously undergoes genome-wide **hypomethylation** and regional **hypermethylation** of CpG islands.

- **Hypermethylation** can lead to the silencing of tumor suppressor genes.
- **Hypomethylation** can lead to impaired genome stability and an increased rate of mutation through chromosomal rearrangements like loss of heterozygosity (LOH).

Thus, DNA methylation has an essential role in all three mechanisms by which cancer cells eliminate tumor suppressor gene function: gene mutation, silencing by hypermethylation, and deletion by LOH.

Epigenetic States and the Environment

DNA Methylation, Aging, and Diet

Because epigenetic states are reversible, they can be modified by environmental factors. In mammals, both hypo- and hypermethylation have been associated with aging. An age-related predisposition to the hypermethylation of CpG islands that can silence tumor suppressor genes may be one factor that increases cancer risk.

Diet is a particularly important determinant. Dietary supplements like folate that affect the supply of methyl groups can influence the rate of disease manifestation and colon cancer incidence. A methyl-deficient diet has been shown to induce liver cancer associated with hypomethylation and enhanced expression of oncogenes.

> To establish a mechanistic link between environmental stimuli and epigenetic states of the genome, a well-defined and sensitive phenotypic readout is required. The coat color gene **agouti** provides such a marker.

The coat color of mice with the *agouti viable yellow (Avy)* allele varies from yellow to mottled to wild-type, caused by the methylation state of a retroviral element inserted into the gene. Wolff et al. found that when pregnant females are fed a diet supplemented with methyl donors, a larger proportion of offspring have a wild-type coat color, which is correlated with an increase in methylation at the *agouti* locus.

> This result argues that an environmental stimulus early in life can change the stable expression of genes and affect the phenotype of the adult... The observations... raise the intriguing possibility that acquired alterations of the epigenetic state may have long-term health effects.

Concluding Remarks

The genetic information of an organism is differentially expressed through mechanisms we are finally beginning to understand. Epigenetic mechanisms constrain expression by adapting regions of the genome to maintain either gene silencing or gene activity. The triggers for this differential marking of the genome are largely mysterious but are yielding to intense study. What needs to be explained is the variety of stimuli that can bring about epigenetic changes, ranging from developmental progression and aging to viral infection and diet. The future will see intense study of the chains of signaling that are responsible for epigenetic programming. As a result, we will be able to understand, and perhaps manipulate, the ways in which the genome learns from its experiences.