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Epigenetics: A Tool to Change the Fate

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Introduction

Epigenetics, which originated in the early 1940s, was introduced by the well-known developmental biologist Conrad Waddington. He discovered that the process of gene interactions in embryological development is intricate. Although the term has a long history, its importance has dramatically increased in recent years. Originating from Aristotelian philosophy, the term itself defines its core: 'Epi' signifying 'over' or 'above,' along with 'genetics' indicating the role of genes.

Conrad Waddington (1905–1975) is known for creating the term epigenetics, which he described as "the field of biology that explores the cause-and-effect connections between genes and their resulting traits, shaping the phenotype." At first, epigenetics studied how genes and their products display characteristics. Today, the centre of attention is on the complex processes by which cells adapt particular shapes or roles and how the traits are inherited through generations of cells.

Epigenetics questions the idea that whether the parental DNA determines the future of offspring. Research has revealed that gene expression is influenced by many factors, such as environment, lifestyle choices, and experiences, without changing the DNA sequence. The findings had significant consequences for the comprehension of illnesses, growth, and adaptation.

Moreover, recent progress has indicated that epigenetic changes can be reversed, creating new possibilities for treatment options. Abnormal epigenetic changes have been found to be associated with diseases like cancer, neurological disorders, and metabolic syndromes.

History

Since its inception, the field of epigenetics has witnessed substantial developments. Going through the timeline of main discoveries, we observe that after Conrad Waddington coined epigenetics in 1942, further research unveiled pivotal insights into the intricate mechanisms governing gene expression.

In 1958, a discovery revealed that environmental influences could have transgenerational effects, concluding that epigenetic changes could be inherited across generations.

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In 1964, researchers identified histone modification, a complex epigenetic mechanism involving the chemical modification of histone proteins around which DNA is wrapped. This discovery showed how changes in chromatin structure could regulate gene expression.

The heritability of epigenetic modifications was found in 2001, demonstrating that these changes could be passed down through cell divisions and even across generations.

This field continued to evolve with high-resolution profiling of DNA in 2007, enabling detailed mapping and analysis of epigenetic modifications across the genome. These milestones have collectively advanced our understanding of epigenetics, showcasing its profound impact on biology and medicine.

Epigenetic Mechanisms

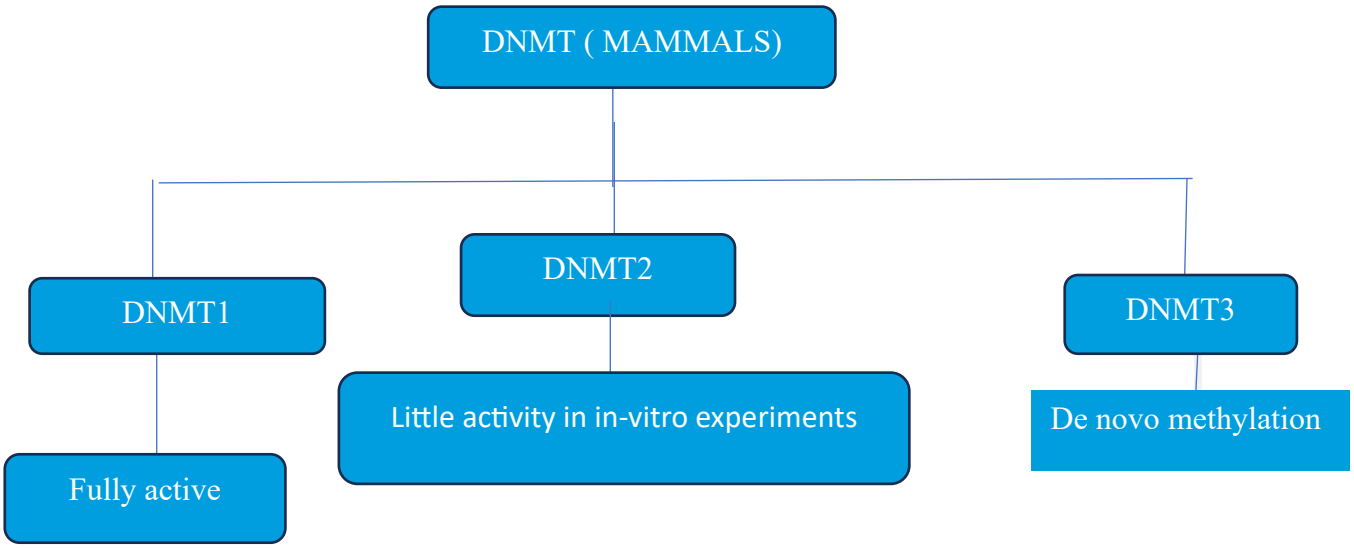
There have been different synergistically acting and complex mechanisms that have been discovered, namely:

- DNA Methylation
- Histone modification
- RNA interference

Among the three of them, there has been a common link between the three of these, i.e., Chromatin and nucleosome. These three mechanisms form a complex layering of transmissible information that the sequences of the bases alone could provide.

DNA Methylation

Methylation is a biochemical process that covalently adds methyl groups to DNA, proteins, and lipids. Methylation is also involved in protein function, DNA repair, and gene expression, as well as plays a vital role in regulatory mechanisms like epigenesis and imprinting. It was found that 5-methyl cytosine is formed due to the addition of methyl group in the 5th carbon of the cytosine ring. This process is catalyzed by the enzyme namely DNA methyltransferase (DNMTs).



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The DNMT family contains DNMT1 and DNMT2, and the DNMT3 subfamily consists of DNMT3a, DNMT3b, and DNMT3L. This category of enzymes is divided into 3 classes, namely:

- Writers – These enzymes catalyse the addition of methyl groups in the cytosine residues.
- Erasers – These enzymes modify and remove the methyl group
- Readers – These enzymes recognize and bind to methyl groups to ultimately influence the gene expression.

The cytosine bases that the methyl targets are located at particular positions, namely CpG dinucleotides. In mammals, nearly all DNA methylation occurs on cytosine residues of CpG dinucleotides. The CpG sites that undergo the methylation process are unevenly distributed throughout the genome of the organism; they form clusters known as CpG islands (Bird A et al., 2002). CpG islands are usually the DNA parts at least 500 bp long with more than 55% content of G and C. CpG islands and neighboring areas within 2 kb are of the greatest significance since their methylation/demethylation effectively changes the expression level of nearby genes. If the methyl group goes and attaches itself to the promoter region of the gene, then it represses the gene action or transcription whereas if it binds to the body of the gene, then methylation promotes the transcription.Interesting fact is that, this methyl moiety can be removed again without changing the sequence content but altering epigenetic pathways.

Classical examples Of DNA Methylation include X Chromosome inactivation, Ageing, gene silencing, genome imprinting, embryological development etc.

Histone Modification

DNA methylation is closely related to the epigenetic mechanism of histone modification. Histone proteins are subject to posttranslational modifications. The histone marks are the result of complex cellular machinery generating local signatures on the DNA sequence they package, thereby establishing an epigenetically transmissible state. The significant histone modifications are acetylation and methylation. The most prominent histone modifications are the serine phosphorylation, lysine's acetylation and methylation, and arginine residue methylation.Histones are usually acetylated at lysine residues by histone acetyltransferases, and the reverse is done by the enzyme called histone deacetylases.Methylation of histones at either lysine or arginine residues is done by histone methyltransferases. A last aspect of histone modifications is their stability. Depending on their chemical nature, histone modifications possess different lifetimes. Whereas phosphorylation is readily reversible through phosphatases, tri-methylated lysine modifications can persist for extended periods.

Process of apoptosis, DNA replication, DNA repair, Cell cycle and transcription are highly regulated by acetylation of histones.

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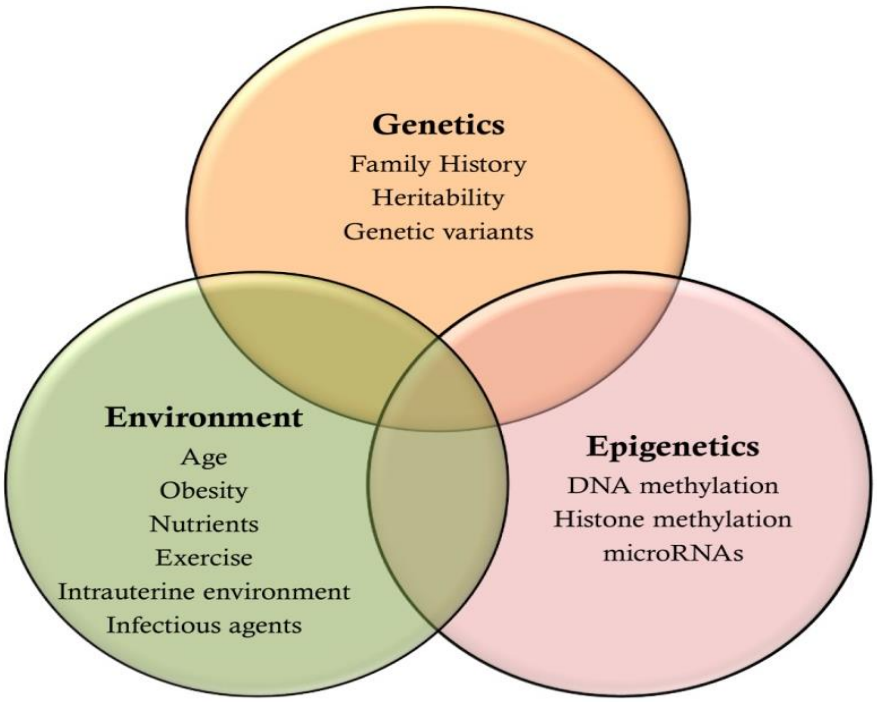
RNA Interference

MicroRNAs (Regulatory noncoding RNAs) regulating expression are usually studied at the post-transcriptional level. The third component, regulatory RNA, plays an ever-increasing yet less well-understood role in epigenetic control, providing an important link between genetic and epigenetic information. MicroRNAs (miRNAs) are small single-strand noncoding RNA molecules, 18–25 nucleotides, which regulate gene expression mostly at a posttranscriptional level. Similar to protein-coding genes, their expression is managed by genetic and epigenetic mechanisms. It is responsible for the diversity of biological processes, including development, apoptosis, cell differentiation, and proliferation (Sampath et al., 2012). With the exception of miRNAs within the Alu repeats transcribed by polymerase III (Borchert, Lanier, & Davidson, 2006), most miRNAs are derived from primary miRNA transcripts (pri-miRNAs) produced by polymerase II, containing a 50 cap and a poly(A) tail. Pri-miRNAs are cleaved within the nucleus by a multiprotein complex called Microprocessor, which is composed of DROSHA and double-stranded RNA-binding domain protein DGCR8/PASHA into 70 nucleotides hairpin precursors known as pre-miRNAs. Pre-miRNAs are further cleaved into mature 22 nucleotides miRNA: miRNA* duplexes by DICER, in association with its partners, TRBP/Loquacious, and PACT in human cells (Hutvagner et al., 2001). Almost 50% of the miRNAs are surrounded by CpG islands. Most miRNAs bind imperfectly to their target sequence and preferentially repress the translational process. These small noncoding RNAs are also implicated in tumor development by regulating the cellular levels of specific oncogenes or tumor suppressor genes (Iorio & Croce, 2012). miRNA control has emerged as an essential regulatory function in animal development, metabolism, homeostasis, and especially the immune system.

Factors Influencing Epigenetic Mechanisms



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Epigenetics Studies in Animals

Cattle

The work on the bovine thymus concluded that enzymes like trypsin can modify chromatin and include DNA methylation and histone modification(Schnedl et al., 1976; Lewis & Chiu, 1980).During normal embryo development, active paternal demethylation of the genome occurs shortly after fertilization, followed by passive demethylation in the maternal genome at the 2- to 4-cell stage and de novo methylation at the 8- to 16-cell stage (Dean et al., 2001; Yang et al., 2007)The histone modification patterns of normal bovine embryos during early embryo development are closely related to those of DNA methylation, which showed demethylation of Histone 3 Lysine 9 (H3K9) and deacetylation at the 2- to 4-cell stage followed by a de novo methylation and acetylation after the 8-cell stage (Santos et al., 2003).

Chicken

Chicken has been used as a model to study epigenetic mechanisms for a very long time. The epigenetic studies of globin gene activation during chicken development provided important insights to understanding human globin gene activation. Both methylation of cytosine and change of chromatin structure can control the expression of globin genes in chickens during development (Haigh et al.,1982). The epigenetic status of genes involved in chickens' disease or pathogen infection is still unclear. Recent work in the laboratory found that the methylation status of several genes was found to be related to the resistance to Marek's disease (MD), which is a chicken lymphoma.

Practical Importance

- Epigenetic markers are used to assess the effects of epigenetic processes on livestock traits, such as productivity, disease resistance, stress response, and reproduction.
- They are also used to identify the genes and pathways involved in the epigenetic regulation of livestock phenotypes (IbeaghaAwemu et al.,2015).
- Epigenetic markers can also mediate the effects of maternal nutrition, fetal programming, and early-life experiences on animal development and health.
- Epigenetics has attracted the animal breeders because it helps find part of the missing causality and missing heritability of complex traits and diseases.
- Breeding companies can also ascertain what genotypes are more susceptible to unfavorable methylation patterns to select animals with reduced susceptibility to unfavorable methylation patterns.
- Farms can also use the epigenetic information to decrease disease incidence and the antibiotics use in livestock productivity.
- It can identify animals with desirable traits or predict their breeding values based on their epigenetic profiles.

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- Epigenetic markers can also be used to manipulate gene expression by using epigenetic drugs, dietary supplements, or gene editing techniques.
- It can also be used to monitor animal health and welfare by detecting epigenetic changes associated with stress, inflammation, or infection.

Challenges

- The main challenge is to find out how epigenetic mechanism worksin successive generation at the cellular level. Unlike DNA, methylation is not constant during an individual lifetime, and environmental forces model methylation over time.
- Another question that arises is what proportion of phenotypic variance does DNAm account for, and how many generations will the current DNAm pattern affect future generations of the lineage.
- Complexity and diversity of epigenetic mechanisms, the lack of standardized methods and protocols for epigenetic analysis, the ethical and social implications of epigeneticinterventions, and the need for more funding and collaboration among researchers (Whelan et al.,2023).
- The scarcity of epigenetic data and resources for livestock species, the difficulty of integrating epigenetic information with genomic and phenotypic data, the uncertainty of the stability and heritability of epigenetic marks, and the lack of causal evidence for the effects of epigenetic marks on animal traits.

Conclusion

Epigenetics has developed our understanding towards gene regulation process, revealing that gene expression can be influenced by environmental factors, lifestyle choices, and experiences without changing the DNA sequence. Since Conrad Waddington introduced the term, epigenetics has evolved into research fields with huge implications for development, disease, and inheritance. Main mechanisms such as DNA methylation, histone modification, and RNA interference define how epigenetic changes regulate gene expression and inheritance. These processes reveal that while our genetic code provides the blueprint, epigenetic factors determine how this blueprint is read and implemented.

Historical milestones in epigenetics, including the discovery of transgenerational environmental effects, histone modifications, and DNA methylation, have deepened our understanding of gene regulation. Practical applications of epigenetics offer new solutions for disease treatment and improvement of livestock traits,increasing productivity, disease resistance, and animal welfare. Despite its significance, the field faces many challenges, such as tracking dynamic changes across generations and compiling epigenetic data with genomic and phenotypic information. Continuous innovation will be essential to cope with these challenges and unlock the full potential

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of epigenetics. In summary, epigenetics provides powerful tools to change the fate of organisms, offering new strategies for disease treatment, agriculture, and understanding the complexities of gene regulation and inheritance.

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