

AYURVEDA AND EPIGENETICS: FOUNDATIONS FOR PREVENTIVE AND PRECISION HEALTHCARE

¹Dr.Aswathy V J, ²Dr.Subin.V R

¹M.D Panchakarma, ²Professor, Department of Panchakarma, VPSV Ayurveda College Kottakkal

Introduction

The quest for a happy and healthy life has driven humanity to explore various ways to understand evolution, creation and maintenance of life. This pursuit was deeply perceived and conceived by the sages of ancient India, leading to the development of *Ayurveda*. *Ayu*, or life, is defined in *Ayurveda* as a manifestation of the union of *Shareera* (body), *Indriya* (sense organs), *Satwa* (mind), and *Atma* (soul), which are integral and interdependent components of life. The main aim of *Ayurveda* is encapsulated in the principle "*Swasthasya Swasthya Rakshanam Aaturasya Vikara Prashamanam*," which means maintaining the health of the healthy and curing the diseases of the diseased. The complete science of *Ayurveda* is summarized in the *Trisutra: Hetu* (causes), *Linga* (signs and symptoms), and *Aushadha* (treatment) for both *Swastha* (healthy) and *Aatura* (diseased), along with *Trayoupasthambhas* (three supports).

Chikitsa, or treatment, in *Ayurveda* includes *Samshodhana* (purification), *Samshamana* (pacification), and *Pathya* (wholesome diet and lifestyle), which encompass *Aahara* (diet), *Vihara* (lifestyle), *Aachara* (conduct), and *Vichara* (thoughts). *Ayurveda* provides elaborate explanations on how to live and what to do or avoid—physically, mentally, emotionally, socially, and spiritually. These factors themselves determine a person's health and disease condition. Traditionally, the understanding of these factors is through *Guna*, *Dosha*, *Dhatvadi* components, and ultimately the *Panchamahabhuta Siddanta*.

Overview of Epigenetics

Epigenetics refers to the regulation of gene expression through modifications to DNA or DNA-associated proteins. Epigenetic regulation includes histone modifications, DNA methylation and non-protein coding RNA. DNA methylation has been particularly focused on environment-mediated changes in health, associated with factors such as environmental chemical exposure, race, gender, and income level. However, epigenetic gene regulation extends beyond methylation alone.

Conrad Waddington introduced the term epigenetics in the early 1940s, defining it as "the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being." In its original sense, epigenetics referred to all molecular pathways modulating the expression of the characters represented by a sequence of genes or the genotype into a particular phenotype. Today, epigenetics is generally accepted as "the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence." Current literature describes epigenetic modifications as including histone variants, post-translational modifications of histone amino acids, and covalent modifications of DNA bases. These modifications are important in determining whether non coding sequences are expressed or not.

Understanding Epigenetics through the concepts of *Ayurveda*

Living organisms are characterised by the presence of DNA which is present in the nucleus of the cell. The DNA molecule is made up of the bases – adenine, thymine, guanine, cytosine – which are arranged in different orders to produce differences among species. Sequences of DNA arranged on specific locations on the

chromosomes make up genes. Out of the approximately 20,000 genes, only less than 2% constitute the genotype of the individual and express themselves¹. These are called the coding genes. The set of stable genes that determines specific characteristics of an individual constitutes the genotype. These undergo changes only in the face of toxic damage. The physical properties as seen in the individual in terms of appearance, attitudes and behaviour is referred to as the phenotype which is produced by the genotype. A person's activities influence the phenotype which in turn affects the expression of the genotype.

The principles of genetic makeup and physical characters can be correlated to the concept of *Prakruti* in *Ayurveda*. *Prakruti* refers to a stable constitution initialising from the single cell stage and continuing to the birth, growth and declining phases of life². Epigenetics offers a contemporary view to understand *Ayurvedic* principles, emphasizing the connection between one's actions and the expression of the genes into the physical characters. Understanding the concept of *Prakruti* and its relation to epigenetic perspectives can help in the application of *Ayurveda* for preventive, promotive and curative effects.

Basics of Epigenetic Mechanisms

Epigenetic mechanisms involve the methods to determine the variations in expression of genes without altering the primary DNA sequence. Number of proteins are involved in the initialisation, activation, and stoppage of the specific triggers that determine the access and translation of DNA sequences to produce growth and differentiation in the embryo and fetus. The different types of epigenetic mechanisms including DNA methylation at CpG dinucleotides, histone modifications, ncRNAs and other complementary mechanisms that control higher-order chromatin organization within the cell nucleus work together to produce the corresponding gene expression. Although DNA methylation, histone modifications, and ncRNAs are important, there is a lot of common ground among the epigenetic marks to regulate the epigenome described below as independent mechanisms, it is important to note that there is cross-talk between these epigenetic marks to regulate the epigenome.

Epigenetic Modifications: DNA Methylation, Histone Modification, and Non-coding RNA

DNA Methylation:

One of the best-studied epigenetic mechanisms is DNA methylation. DNA methylation leads to silencing of the genes as the access of gene promoters to activate the translation process is affected. This is achieved by binding of methyl group to DNA and also by histone modifications. In eukaryotic species, the addition of a methyl group to the cytosine of the CpG dinucleotide is called DNA methylation. A major part of the DNA methylation occurs in parts of the genome called CpG islands which are concentrated regions of CpG nucleotides. The patterns of DNA methylation are established and maintained by specific proteins like DNA methyl transferases.³

Histone Modifications:

Chromatin is the complex of chromosomal DNA and proteins, and DNA is packaged in chromatin around histone protein units called nucleosomes. Histones are highly alkaline and positively charged due to amine groups, which help them interact with and bind to the negatively charged phosphate backbone of DNA. During acetylation, amines on the histone change into amides, neutralizing the positive charges on the histone and reducing their binding capability with DNA. This results in chromatin expansion, allowing genetic transcription. Histone deacetylation is catalyzed when histone deacetylases remove acetyl groups, increasing the positively charged amine groups on histones and reducing transcription.⁴

Non-coding RNAs:

Long non-coding RNAs can silence genes, while microRNAs (miRNAs) are small non-coding RNA molecules containing 20–24 nucleotides. Around 900 miRNAs have been identified, and it is estimated that they control approximately 30% of human protein-encoding genes. miRNAs function in RNA silencing and post-transcriptional regulation of gene expression by degrading messenger RNAs and inhibiting protein translation.

Epigenetic influence in diseases

As seen above, addition of methyl groups to the DNA is a common and widely used mechanism for epigenetic modifications in cells, closely linked to various human diseases, including cancers, autoimmune disorders, and neurological conditions like Fragile X syndrome, Huntington's, Alzheimer's, Parkinson's, and schizophrenia. Methylation's role extends to complex diseases influenced by secondary factors such as sex differences and age, potentially altering disease severity.

Epigenetic modifications significantly impact cancer development. For example, hypermethylation of promoter regions in tumor suppressor genes can deactivate many tumor-suppressing functions, contributing to cancer progression. Recent studies have also confirmed the dysregulation of miRNAs in breast cancer, highlighting their potential as diagnostic biomarkers.

In autoimmune diseases, concordance studies in both monozygotic and dizygotic twins suggest a significant role for epigenetic factors. Many functions of immune cells, such as hematopoietic lineage determination, antigen-receptor rearrangement, allelic exclusion, and inducible immune responses against pathogens, are controlled epigenetically. Alterations in these epigenetic mechanisms regulating immunological development can promote autoimmune diseases, underlining the importance of epigenetics in understanding and potentially treating these conditions.

Factors Influencing Epigenetic Changes: Environment, Diet, Lifestyle

Epigenetics encompasses the processes that influence gene expression throughout an individual's lifespan, including prenatal and postnatal stages, childhood, social experiences, diet, nutrition, toxin exposure, lifestyle, behaviour, environmental factors and stress which collectively influence gene expression, resulting in the dynamic and ever-changing expression of physical characteristics in an individual⁵. The specific parts of DNA that are expressed can vary based on past exposures and experiences, which are embedded in the genes through epigenetic modifications⁶.

Researches indicate that the structural and functional changes in cells can be due to environmental factors that can modify gene expression via epigenetic mechanisms including silencing of tumour suppressor genes by toxicants like diesel exhaust particles, cigarette smoke and inorganic arsenate which leads to carcinoma. Chronic sun exposure also causes epigenetic changes, such as hypomethylation in the skin as age increases. Epigenetic changes have a transgenerational impact. Future generations can be affected by dietary issues, exposure to pollutants and stress with epigenetic alterations being transmitted to the developing embryo. Nutritional abnormalities, environmental toxicants, and stress can promote epigenetic alterations that are transmitted to subsequent generations, potentially resulting in disease⁷.

The components of diet which are all bioactive exert their influence on gene expression. They can regulate different epigenetic mechanisms like DNA methylation, histone modifications and chromatin remodelling. They can also produce changes in miRNA expression⁸.

Stress exposure can alter epigenetic marks and influence gene expression. The changes produced by stress on gene expression are seen in depression.⁹ Negative and positive emotions have varying effects on DNA. Anger, stress, frustration and fear create the similar tightness in the DNA that it causes in the somatic systems also. Similarly positive emotions cause relaxation of the DNA and expression of the genetic code¹⁰.

Epigenetics in development, age and reversibility

Epigenetic changes begin before birth, influencing gene expression throughout life. While all body cells contain the same genes, have unique structures and functions. For example, muscle cells and nerve cells share the same DNA but function uniquely due to these epigenetic modifications.

Epigenetics also play a role in aging. The level of DNA methylation decreases with age. Newborns have the highest levels of DNA methylation, while 103-year-olds have the lowest. Not all epigenetic changes are permanent; some can be added or removed in response to changes in behaviour or environment. For instance, smoking can result in epigenetic changes, such as hypomethylation in smokers. However, after quitting smoking, methylation levels can gradually return to those similar to non-smokers.

Case Studies and Research Evidence

Epigenetics and Diet

Researches have tried to identify the chances of obesity by studying the genes involved in adipogenesis. The methylation changes in obesity and inflammation related genes also are important⁶. Curcumin, a component of turmeric (*Curcuma longa* L.), has been identified to promote tumour suppression activity in Hodgkins lymphoma and breast cancer cells by histone modifications¹¹. Components of food like green tea, grapes, soyabean and cruciferous vegetables also have epigenetic effects. Their bioactive principles like polyphenols, genistein and isothiocyanates have been studied in this regard¹². Withaferin A which is a component of Ashwagandha (*Withania somnifera*), has been shown to reduce DNA methylation and histone modifications in breast cancer cells and cause their apoptosis¹³.

Epigenetics and Lifestyle

Physical activity increases methylation in LINE – 1 elements which counters inflammatory responses and chromosomal instability⁶. A study on men with prostate cancer showed that expression of 500 genes was altered by lifestyle intervention programme, meditation, breathing exercises, aerobic exercise and a vegetarian diet. The downregulated genes were involved in tumour formation¹⁴. Lifestyle modifications with the inclusion of aerobic exercises and vegetarian diet resulted in expression of genes reducing cardiovascular risk¹⁵. Additionally, stress reduction programmes through meditation and lifestyle increased telomerase gene expression in hypertensive patients¹⁰.

Exposure to smoke, pollutants, alcohol and psychological stress can produce nuclear changes including histone modifications, hypomethylation, miRNA expressions with these changes simulating those seen in cancer cells. The role of stress on gene expression is indicated by the hypermethylation changes in glucocorticoid receptor gene in suicidal tendency in people with a history of child abuse. Changes in circadian rhythm also affects gene expression as seen in night shift work which causes methylation changes in inflammatory genes⁶.

Intersection of Epigenetics and Ayurveda

The unique concept of *Prakriti*, which represents the physical expression of distinctive genetic codes, provides insight into natural immunity or *Sahajabala*. This determines an individual's susceptibility to diseases. While genetics as a field emerged in the mid to late 19th century, *Ayurvedic* scholars had already acknowledged the formation of *Garbha* (embryo), the role and transmission of inherited factors, congenital anomalies, and hereditary disorders centuries earlier. The Ayurvedic concepts of *Beeja*, *Beejabhaga*, and *Beejabhagavayava* explain the transmission of genetic material across generations.

Garbhotpadaka Chaturbhava (including *Ritu*, *Kshetra*, *Ambu*, and *Beeja*) and *Shadbhava* (six procreating factors) play crucial roles in preventing birth defects and genetic disorders. Daily routines (*Dinacharya*), seasonal regimens (*Ritucharya*), codes of conduct (*Sadvrittha*), the management of suppressible and non-suppressible urges (*Dharaneeya* and *Adharaneeyavega*), rituals preparing women for conception (*Ritumaticharya*), and antenatal care (*Garbhinicharya*) help maintain the balance of *Dosha*, thus regulating gene sequencing and expression.¹⁶

Epigenetics explores how factors throughout life stages—such as prenatal and postnatal periods, childhood, social experiences, diet, nutrition, toxin exposure, lifestyle, behavior, stress, and environment—influence gene expression. Phenotypic expression varies among individuals based on which DNA parts (genes) are expressed, shaped by past exposures, experiences, and impressions. These epigenetic modifications are embedded in the genes.

Phenotypes are dynamic and ever-changing. If proper principles are not adhered to, health alterations and disease manifestation occur. Ayurveda extensively addresses these preventive measures and health promotion principles in the contexts of *Maturaaharavihara*, *Sadvritta*, *Dinacharya*, *Ritucharya*, *Na Vegandharaneeya*, and *Matrashiteeya*. These principles are vital for disease prevention and health promotion.

Ayurgenomics is a pioneering field that integrates Ayurveda with genomics, aiming to identify genomic correlations with *Prakriti* phenotypes described in *Ayurveda*.¹⁷ Ayurvedic genetics uses terms such as *Beejabhaga* (chromosome), *Beejabhagaavayava* (genes), and *Beeja* (sperm/ovum) to explain its concepts. Gene expression

reflects cellular functions, while genetic variations can lead to mutations and changes in gene frequencies, influencing an individual's phenotype (DNA).

Pharmacogenetics explores the genetic basis underlying population differences in drug responsiveness, aiding in the scientific understanding of variations in the human genome. These genetic variations are crucial for understanding adverse drug reactions and disease conditions. The core principle of *Ayurveda*, emphasized by Charaka around 4000 years ago, is that each patient is unique and should be treated as such. In disease contexts, *Ayurveda* attributes etiological factors primarily to *Ahara* (diet), *Vihara* (lifestyle), *Manasika Nidana* (psychological factors), and others like *Agantuja Nidana* (external factors) and *Karma*.

Epigenetics is believed to be integral to *Ayurveda*, as it merges genotypic and phenotypic variations. *Ayurveda* identifies factors such as behavior, lifestyle, stress, diet, digestion, and environment as influences on *Deha* (body) *Prakriti* (psychological and physiological composition), which is related to phenotype, and *Janma* (birth) *Prakriti*, which is related to genotype. Understanding these factors can improve interaction and comprehension within the healthcare system, fostering greater connectivity between both fields of science for optimal health outcomes

Prakriti and Vikriti in Ayurveda

Prakriti, which is fixed at birth, remains constant throughout one's life, independent of ethnic, racial, or geographical factors. It provides a suitable method for categorizing phenotypes for genotyping. *Vikriti*, on the other hand, refers to disorders of *Deha Prakriti* in modern medicine. At the molecular level, it is suggested that tRNA, proteins, and mRNAs exhibit properties and characteristics reflecting the three Ayurvedic dosha—*Kapha*, *Pitta*, and *Vata*.¹

Genetic Factors and Ayurvedic Concepts

Acharyas explained *Beeja*, *Beejabhaga*, and *Beejabhagaavayava* with the help of certain diseases. When *Beejabhaga* in the ovum of the mother, which is responsible for the production of *Garbhashaya*, is excessively vitiated, she gives birth to a *Vandya* (sterile child). Similarly, when the *Beejabhagaavayava* in the ovum responsible for the production of the uterus is excessively vitiated, she gives birth to *Puthipraja* (a child who delivers a dead fetus). Vitiating *beeja*, i.e., *Shukra* and *Shonita*, causes fetal defects.⁴ Diseases like *Prameha* and *Kushta* are said to be caused by *Beeja dushti*, which later manifest in adult life. *Ayurveda* also mentions *Garbha upgahaatkara bhaava*, factors causing abnormalities to the foetus, including intercourse, exertion, trauma, journey, staying awake at night, suppression of urges, fasting, abnormal postures, and hearing unpleasant sounds.¹⁸

Garbhopaghatakarabhava: Precautions for Pregnant Women

Ayurveda advises pregnant women to take precautions concerning diet and activities to avoid physical and mental strain. She is advised to avoid excessive exercise, pungent materials, harsh or violent activities, as these can disfigure placental formation and affect the nutritional flow through minute channels.¹⁹

Ritumatcharya , Garbhinicharya, Douhrida

From the first day of menstruation onwards, a woman should follow specific do's and don'ts, such as avoiding sleeping during the day, to regulate the *Tridosha*. *Garbhinicharya* ensures non-exposure to toxins, chemicals, dosha-provoking *Aharavihara*, and ensures proper growth and development of the foetus. The concept of "*Douhrida*" in *Ayurveda* highlights the significance of fulfilling the desires of a pregnant woman (*Garbhini*) and its impact on the developing fetus.⁷ This ancient idea aligns with modern understandings of rapid brain growth and myelination that occur between the 13th and 20th weeks of development. Epigenetic mechanisms play a crucial role in the process of demyelination, emphasizing the importance of epigenetic regulation of myelination in both health and disease.²⁰

Masanumasika Pathyakrama (Month-wise Dietary Regimens)

A healthy diet should be taken at proper times and in a proper manner to keep the *Tridosha* balanced. Month-wise diets and regimens are explained for pregnant women. Following such diets ensures proper nourishment, thereby avoiding intrauterine growth restriction (IUGR).²¹

Ayurvedic Approach to Motherhood

Ayurvedic approaches to pregnancy and childbirth are holistic, including proper diet, behavior, activities, and spiritual actions. For obtaining healthy progeny, six procreative factors (*Shadgarbhakarabhavas*) are explained: *Matrija* (maternal), *Pitrija* (paternal), *Atmaja* (soul), *Rasaja* (nutritional), *Satmyaja* (wholesomeness), and *Satvaja bhava* (psyche/mind). The confluence of these factors is essential for healthy offspring.¹⁸ A healthy mother and father (with good conduct), the practice of a wholesome regimen, and a healthy mind play prime roles in achieving beneficial epigenetics in the offspring. Ahara (diet) is considered one of the three sub-pillars in Ayurveda (*Thrayo-Upasthamba*).²² Ayurveda emphasizes basic dietary guidelines, including appropriate food combinations, cooking methods, storage, eating atmosphere, hygiene, and etiquette (*Ashtavidha Ahara Vidhi Visessa Ayatana*). The preventive and curative aspects of Ayurveda revolve around the central theme of *Pathya Ahara-Vihara and Sadvritta*.

Final Thoughts on the Synergy of Epigenetics and Ayurveda

The development of scientifically designed tools has revolutionized the approach to detoxifying the body, effectively removing toxins at both macro and micro levels. This micro-level action can be attributed to advancements in various domains, including metabolomics, genomics, and biomics.²³ A notable emerging concept in this field is Ayurgenomics, which integrates traditional Ayurvedic principles with modern genomic insights to enhance personalized healthcare. By leveraging these interdisciplinary tools and approaches, we can better understand and support the body's natural detoxification processes.

Panchakarma procedures, such as *Virechana* and *Vasti*, can be further explored with future analytical studies on gene analysis, potentially paving the way for future genomic studies. These procedures play a role in altering epigenetic changes caused by lifestyle and diet, highlighting the potential for integrating traditional practices with modern scientific advancements.

Conclusion

Epigenetics, defined as somatically heritable states of gene expression resulting from changes in chromatin structure without alterations in the DNA sequence, encompasses DNA methylation, histone modifications, and chromatin remodeling. The choices we make in diet, perception, actions, and environment can directly impact our genes through these epigenetic processes. Modern research, such as the study on DNA methylation in monozygotic and dizygotic twins, supports the idea that epigenetic factors contribute to phenotypic similarities, echoing ancient wisdom that microenvironment factors influence gene expression.

Ayurveda has long recognized the influence of various factors on health and disease, including congenital birth defects, and offers treatments like *Beeja shuddhi* and *Garbhini paricharya* to maintain maternal and child health. These traditional practices can be understood through the lens of epigenetics, which reveals how modifiable factors influence gene expression and can be managed to avoid adverse health outcomes. By following Ayurvedic principles such as *Dinacharya*, *Ritucharya*, and *Garbhotpadakachaturbhava*, couples can optimize their health and increase the likelihood of producing healthy progeny.

Future of Integrative Health Approaches

Garbhini Paricharya, or Ayurvedic antenatal care, represents a preventive approach in maternal health that holds promise for therapeutic applications. This integrative method offers the potential in managing severe disease conditions during pregnancy. Moreover, differential gene expression studies related to *Garbhini Paricharya* could pave the way for future research, providing deeper insights into its effectiveness and mechanisms.

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