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Epigenetics: Understanding How our Choices Lead to our Diseases

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Abstract

Epigenetics, a fairly new scientific field is uncovering how modifiable factors such as diet and lifestyle can alter genes on a chemical level and the subsequent gene expression for certain diseases. Epigenetics broadly studies the ways in which genes can be altered without changing the DNA sequence itself. This article will first equip the reader with background knowledge regarding the emergence of epigenetics and what epigenetic mechanisms have been discovered in association with changes in gene expression. Finally, this article will discuss current research that focuses on how environmental influences throughout an organism's life can modulate the susceptibility and prevention of chronic diseases through epigenetic events. Our diets and lifestyle choices are also an integral part of reaching optimal health.

Keywords: Epigenetics; Genetics; Nutrition; Exercise; Health; Disease; Lifestyle

Introduction

Nearly half of the adult U.S population, 117 million people, lives with one or more chronic disease today, according to the Center for Disease Control. Seventy-five percent of the total U.S health care budget, amounting to almost $1.5 trillion dollars per year is spent on chronic diseases such as diabetes, heart disease, stroke, cancer, obesity, and asthma [1]. On a global scale, chronic diseases are now the leading cause of morbidity and mortality and are becoming a serious burden for both developed and developing countries [2]. While the global prevalence and related costs have become impossible to ignore, often times what is forgotten is that well over half of these diseases are preventable through modifications to lifestyle and health behaviors such as diet, exercise, or other environmental exposures [1].

Epigenetics, a fairly new scientific field, targets the particular chemical pathways through which these modifiable factors such as diet and lifestyle choices can alter gene expression, determining the onset and development of chronic diseases. The chemical molecules involved in these pathways that alter gene expression independent from changes in the DNA sequence can be naturally produced by our bodies, consumed through our diet, or we can be exposed to them through the environment. This article will outline the emergence of the epigenetic field and the epigenetic mechanisms discovered to be associated with changes in gene expression. The majority of the article will then discuss current research that focuses on how environmental influences throughout an organism's life can modulate the susceptibility and prevention of chronic diseases through epigenetic events.

The Emergence of Epigenetics

In 1808, Jean-Baptiste de Lamarck provided one of the first theories for evolution, proposing that an organism could pass on traits acquired in its lifetime to its offspring [3]. Based on observations, Lamarck theorized that the environment had the greatest influence on the evolution of species over time as those characteristics that were useful to a particular organism were retained and passed on to offspring while those characteristics that were not useful were lost in future generations [4]. For example, according to Lamarck's theory of evolution, the long neck of the giraffe was developed as an adaptation to the environment; as they stretched their necks to reach the leaves on the tallest trees, their necks gradually lengthened and the offspring acquired longer necks over time, through this mechanism called 'soft inheritance' [5]. 'Soft inheritance' hypothesized that traits did not remain constant between different generations; instead they changed in response to environmental influences.

However, scientific contributions during the 19th and early 20th centuries including Darwin's theory of natural selection, Mendelian genetic theory, and Weismann's theory of germplasm, led to the emergence of the theory of 'modern evolutionary synthesis' [6]. The 'modern evolutionary synthesis', as opposed to Lamarck's theory of evolution, was supported by experimental data from several branches of biology and it was rooted in 'hard inheritance' which assumed that hereditary material remained constant and was inherited through DNA in the form of genes [7,8]. While the 'modern evolutionary synthesis' based in 'hard inheritance' has provided the foundation for biological fields today, recently, Lamarck's simple observation of 'soft inheritance' has been a motivation for a field of genetic study called epigenetics. The word epigenetics directly translates to "above genetics" and today it encompasses the study of any change in phenotype or gene expression caused by molecular mechanisms other than changes in the DNA sequence [9-12].

A great illustration of an epigenetic process is observed in eusocial insects such as the honeybee [13]. As larvae, the honeybee queen and the worker bees are genetically identical, but the queen bees live for one to three years and produce up to 2,000 eggs per day while the worker bees are sterile and their lifespan is less than two weeks. The differences start after hatching, as the larvae who are fed small portions of pollen and nectar become worker bees and constantly work to clean comb cells and forage for food while the larvae fed 'royal jelly' in large quantities for long periods of time become the queen bees and do not engage in any work. Thus, while both the queen bees and the worker bees have identical genetic information as larvae, it has been elucidated through recent genomic studies, that the different diets and

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activity levels of the honey bees induce changes in the expression of particular gene pathways for development [14]. This example along with current epigenetic research involving animal and human models reinforce that soft inheritance, the generation of a phenotype that is not rigidly determined by DNA, can be modulated by diet, activity level, and other environmental stimulants [15]. Additionally, one of the most fascinating facets of epigenetics is 'transgenerational epigenetics' which involves phenotypic traits that are not genetically determined that are passed onto future generations. Thus, because epigenetic modifications alter gene expression but not the DNA sequence itself, studying the specific epigenetic mechanisms as well as the physiological and transgenerational effects of epigenetics can reveal biomarkers for disease susceptibility, detection, and prevention.

Specific Epigenetic Mechanisms

The genome contains all of the information for the proper physiological and psychological functioning of an organism. However, regulation is necessary in order to express the proper genes at the proper times and in proper order and correct tissues in that organism. For example, gene silencing occurs during gamete development where some genes are imprinted by the methylation of DNA and are not expressed. Imprinting of genes is gender and individual specific, thus, offspring inheriting one copy of an imprinted gene from one parent and a non-imprinted gene from the other parent will only express the latter [16]. DNA methylation is just one example of an epigenetic 'mark' or 'tag'. The other well studied biological processes that modulate epigenetic events include histone modification, and non-coding RNA.

DNA methylation constitutes covalent additions of methyl groups often at the 5' position of a cytosine ring in eukaryotes [17-19]. While the methylation pattern of the parent DNA serves as a template for the newly synthesized DNA, methylation processes can also occur at sites along the nucleotide that were previously unmethylated. This process is called 'de novo methylation' and when it occurs at promoter regions it is usually associated with the underexpression or silencing of genes [20-22]. However, hypermethylation sometimes prevents the binding of inhibitory factors so it can result in overexpression of certain genes as well [23].

Histone modification, a second epigenetic mechanism, can include the methylation, acetylation, phosphorylation, ubiquitination, and ADP ribosylation of chromosome packaging proteins [24]. These molecular changes alter the level of condensation of the chromatin, thus, defining the area that is accessible for transcription [25-27].

Non-coding microRNAs (miRNAs) also play a role in epigenetic regulation by interfering with the expression of several important proteins responsible for DNA and histone methylation and acetylation. Typically, these miRNAs are less than 25 nucleotides in length and they interfere post-transcriptionally with RNA by repressing the expression of hundreds of target genes [28,29]. Self-sustaining loops and structural inheritance also impact epigenetic events but these mechanisms are less understood and will not be discussed in length in this article. Instead, the focus will remain on how DNA methylation, histone modifications, and noncoding RNA act in concert to make molecular modifications to DNA contributing to disease susceptibility and expression [10,30,31].

Epigenetic Mechanisms that Impact Disease Development

Epigenetic research has significant potential for improving the detection of disease risk and possible disease prevention strategies, specifically, by targeting the complex interactions between diet, lifestyle, genetics, and disease. Epigenetic changes occur most often during gestation, neonatal development, puberty, and old age [9]. However, animal studies and human epidemiologic data suggest that long-term epigenetic changes that manifest in disease phenotypes are especially critical during the prenatal and neonatal stages as well as during times of 'dietary transition' in adulthood [32-35].

Early Life Programming for Disease Susceptibility

The link between the fetal environment and development of several chronic diseases was originally observed by David Barker in the early 1900's and is often described as the 'Developmental Origins of Adult Health and Disease Hypothesis' (DOHaD) or the 'fetal programming hypothesis'. His studies utilized birth weight as a marker for intrauterine nutrition and showed an inverse relationship between birth weight and risk of hypertension, cardiovascular disease, and type II diabetes in adulthood [36,37]. Countless studies have supported the DOHaD and have confirmed that environmental stimuli such as nutrition during fetal development can lead to an increased risk for developing various chronic diseases during adulthood by permanently modifying the expression of genes involved in cell structure and function [38-40]. Offspring of mothers who were severely undernourished during the Dutch Famine of 1944, showed reduced glucose tolerance, raised insulin concentrations at age 50, double the incidence of cardiovascular disease, and a five-fold increase in risk of breast cancer in offspring later in life as compared to controls [41,42]. Importantly, it was interpreted through these famine cohort studies that severe calorie restriction during early gestation had greater adverse health effects than restriction in later pregnancy periods [43]. Today, the periconception period of pregnancy has been identified as the most sensitive period to poor maternal nutrition because certain epigenetic modifications from the egg and sperm can be erased and new marks are established for long-term epigenetic reprogramming [44,45]. In contrast, in selected cases of transgenerational epigenetic inheritance, the epigenetic modifications are inherited and not removed or cleansed at conception. Both cleansing and inheritance are possible; we do not know why they are cleansed in some cases and not in others.

Not only is sufficient calorie intake important, but the quality of the calories ingested is just as critical in shaping the epigenome of offspring and preventing disease. One experiment examined how maternal nutrition could alter the expression of the agouti gene in mice. The agouti gene, a homolog of which is also found in humans, codes for a brown coat color in mice and low disease risk when methylated and codes for a yellow, obese mouse prone to diabetes and cancer when the gene is unmethylated. The human homolog is found in adipocytes and leads to abnormal fat metabolism. The results showed that the pregnant mice that were fed a methyl rich diet gave birth to mostly brown healthy pups that remained healthy for life [46]. Discoveries such as these imply that optimal nutrition during pregnancy should include methyl-donor nutrients such as folic acid, B vitamins, and S-Adenosyl-L-Methionine (SAM-e) that can prevent or reverse epigenetic changes due to methylation modifications that could manifest in disease phenotypes later in life [47,48].

Another contribution which has been elucidated through an ovine model has shown that maternal undernutrition can lead to the hypomethylation and increased histone acetylation of certain promoters in hypothalamic peptides that regulate the appetite and energy expenditure in offspring. Other consequences of maternal undernutrition are disturbances in skeletal muscle development and increased visceral fat deposits in offspring, which correspond to DNA methylation patterns of particular gene promoters in rat models [49-52].

In addition to the effects of maternal undernutrition, there is a growing wealth of experimental evidence revealing that maternal obesity and high fat diets lead to the predisposition for chronic metabolic deficiencies in offspring. For example, maternal high fat diets have thus far been associated with life-long hyperglycemia, insulin resistance, increased fat deposition, and obesity in offspring [53]. In certain studies, independent maternal obesity or diabetes status, maternal high fat diet during pregnancy alone, has led to diabetes related conditions in offspring such as impaired glucose tolerance of the B-cells and impaired insulin secretion of the pancreas [54].

Paternal effects also have a significant role in affecting offspring development as demonstrated through several animal models such as fruit flies, mice, non-human primates, and humans [55-57]. For example, human studies have uncovered a relationship between paternal obesity and changes in sperm count, concentration, motility, and morphology that lead to an increased possibility of sperm DNA damage [58]. One cannot blame mothers or fathers as each may confer transgenerational effects.

Studies within the past year have identified that paternal obesity is also associated with hypomethylation of the imprinted insulin-like growth factor gene (IGF2) in offspring which can result in malfunctioning of many physiological processes, potentially leading to chronic diseases in adulthood [59]. Additionally, low birth weight in both male and female offspring as well as higher levels of adiposity, B-cell dysfunction, and risk of diabetes in female offspring have been linked to paternal high fat diets [60,61].

Compelling studies also indicate that intrauterine exposure to chemical toxicants during pregnancy such as cigarette smoke, alcohol consumption, and antibiotics have all been associated with low birth weight, and DNA methylation modifications [62-64] (Figure 1).

Impacts for Disease Susceptibility during Adult Development

Epigenetic research involving monozygotic twins, who are born with identical genomes, yet exhibit different phenotypes later in life, are an excellent example of how impactful environmental factors can be in the developmental plasticity of organisms. These identical twin studies have demonstrated a correlation between phenotypic differences such as disease with changes in DNA methylation patterns [65]. Similar to nutrition during pregnancy, nutrition during adult development is a key environmental signal that can be integrated into the genome and can cause changes in gene expression of health and disease phenotypes [66,67]. This dynamic relationship between nutrition and genes throughout an organism's lifetime has now been recognized as a subfield called Nutritional Epigenomics or 'Nutrigenomics' and provides promising insight for how to target disease from a nutritional standpoint [68].

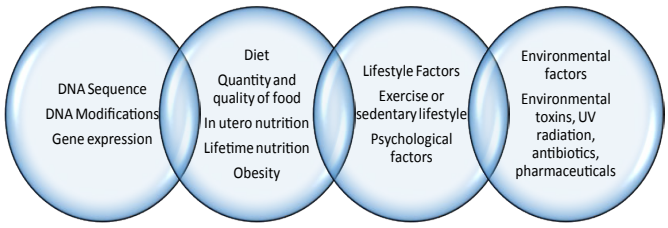

Figure 1: Example showing epigenetic factors involved in health and wellness. Understanding how our choices may determine our health or disease states. How our choices in personalized nutrition, lifestyle factors, exercise, various environmental exposures, or various parental choice factors may determine the health and wellness outcomes of ourselves or our offspring across several generations.

In adults, the most critical times that dietary factors can influence the epigenome are during periods of "Dietary Transition" in which either an excess or deficiency of certain nutrients are consumed (protein deficiency, caloric restriction, or chronic high fat feeding) and last for a long duration of time [69-71]. These changes can be subtle, may be expressed over long periods, or may result in permanent changes in gene expression as in the case with most epigenetically associated changes for disease risk. Chronic high fat feeding has been shown to alter the DNA methylation pattern of genes that regulate food intake in mice, contributing to the development of obesity and obesity related illnesses [70]. Also, possible transgenerational effects of high fat feeding have been explored in recent studies and results from animal models suggest that epigenetic modifications can accumulate in successive generation leading to predisposition for metabolic phenotypes such as lipogenesis or beta cell dysfunction and may be functions of the human agouti homolog gene [72].

Caloric restriction, on the other hand, has shown a positive correlation with disease prevention by increasing lifespan and delaying the onset of cardiovascular disease, type II diabetes and forms of cancer [73,74]. Recent data supports that caloric restriction results in chromatin remodeling which leads to lifespan extension, and it reverses onset of these aging-related degenerative diseases by stabilizing the genome through various epigenetic mechanisms [75]. There are also many chemicals and additives that contribute to epigenetic modifications upon exposure, and can lead to physiological changes. One well documented scientific example that has also gained popularity through the media, is exposure to Bisphenol A (BPA), a compound found in polycarbonate plastic that alters the epigenetic programming leading to endocrine disruption which can increase risk for diabetes, cancers, reproductive problems, early puberty, and obesity [76,77].

Exercise has also been known to be a protective factor against the risk of cardiovascular disease, cancer, and type II diabetes by altering the gene expression in multiple tissues. Recent epigenetic studies have uncovered that increased levels of physical activity results in the methylation of individual genes and global methylation remodeling which contributes to changes in metabolic function associated with the decreased risk of chronic diseases [78-81]. For example, exercise has shown to alter the expression of genes involved in improved lipid and glucose metabolism as well as muscle tissue, leading to improvements in glucose homeostasis and decreased blood pressure [82-89]. These changes have been linked to exercise-induced molecular modifications such as the hypomethylation of skeletal muscle genes, changes made to the actions of cytosolic messengers such as calcium and AMP, as well as the increased expression of the GLUT4 gene [78,83,84]. Exercise has also shown to protect against inflammatory environments which promote carcinogenesis and the development of other age-related diseases by decreasing the expression of the ASC gene through upregulating methylation [85,86]. Results from a six month exercise intervention performed this past year have also helped to support that the DNA methylation of many genes in both skeletal muscle and adipose tissue change in response to exercise [87]. In a contrasting study in which subjects were to mimic the sedentary lifestyle of today's society by participating in nine days of bed rest, the opposite results of the exercise intervention study were found to be true [88]. Not only has exercise been studied as prevention for chronic disease but there

is promise for the use of exercise as forms of treatment as well. The beginnings of this type of treatment experimentation suggest that regular exercise can affect epigenetic regulation of tumor suppressor genes in cancer patients, and decrease susceptibility to several diseases associated with chronic inflammation such as type II diabetes, arthritis, and atherosclerosis [89,90].

Conclusion

Epigenetics research offers us a vehicle to better understand the many aspects of diet, lifestyle factors, exercise, and environmental factors that contribute to chronic disease prevalence and susceptibility, specifically those aspects that are not rigidly determined by our genes but those that we have control over. This article has detailed the recent evolution of the field of epigenetics as well as current knowledge regarding how the biological mechanisms that regulate gene expression are correlated with the expression of disease phenotypes. The stages of life most vulnerable to epigenetic change as well as the most influential environmental factors that lead to these changes have also been identified. However, there is much more to discover, especially, regarding the permanence of epigenetic changes and the ability to transfer those alterations, trangenerationally. The field of epigenetics offers alternative disease treatment discoveries that could lead to the better management of chronic diseases through prevention tactics such as nutrition and exercise interventions as well as drug development that specifically target the epigenetic pathways and reverse epigenetic marks associated with disease. Arguably, the most important contribution is that epigenetic research has provided a molecularly based incentive for individuals and populations to invest in healthy nutrition and lifestyle behaviors to improve health outcomes for individuals presently and for future generations.

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