

# Epigenetics and the exposomes: Obesity and beyond

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## ABSTRACT:

The specific genetic alterations that result in diseases and complex syndromes have been and continue to be identified. Search for the origins of disease have led to investigations into the roles of dietary and environmental factors as potential triggers or modifiers of risk. Genome-wide association studies have identified concepts such as the rare variant-common disease hypothesis and the common variant-common disease hypothesis.<sup>1</sup> Through association studies, unique gene-environment interactions, which may occur with or without specific periods of permissiveness or vulnerabilities, have also been identified. Major conditions where the role of exposomes and epigenetics are rapidly evolving are obesity, neurological disorders, immune disorders and cancers. These concepts are particularly intriguing in the context of obesity.

## BACKGROUND:

Epigenetics can be defined as heritable traits resulting from changes in DNA or chromatin structure without alterations in the DNA sequence.<sup>2</sup> Nutritional epigenetics is seen as a means for the prevention of developmental diseases and cancer, and to delay processes associated with aging.<sup>3,4</sup> Diseases in which epigenetic factors are considered significant include type 2 diabetes mellitus, obesity, inflammation, cardiovascular diseases, neurocognitive disorders, and immune diseases, with neural function influenced by environmental factors including early experience.<sup>5</sup> Studies with rodent models suggest that during both early development and in adult life, environmental signals can activate intracellular pathways that directly remodel the epigenome, leading to changes in gene expression and function. These studies define a biological basis for the interplay between environmental signals and the genome in the regulation of individual differences in behavior, cognition, and physiology.<sup>6</sup> In reproduction, certain genes are turned on while others are turned off in the process of imprinting. In the case of imprinting, even though there are two copies of the gene, only one copy is expressed and there is no substitute functional allele. For this reason, imprinting makes the imprinted genes more vulnerable to the negative effects of mutations.<sup>7</sup>

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## EPIGENETICS:

Epigenetics involves the study of heritable changes in gene expression that are not due to changes in the nucleotide sequence, but involve other mechanisms such as histone modifications or changes in DNA resulting from alterations in the methylation patterns. Such modifications can be impacted by diet, nutrients, and environmental factors such as chemical, psychological, and behavioral factors. While the role of dietary factors is more readily understood in the context of obesity, the epigenetic phenomena associated with obesity risks provides the linkage between factors such as stress, sleep deprivation, and obesity.

## EXPOSOME:

Exposome is a term used to define the sum of all of the individual's exposures and to evaluate the impact of such exposures on health outcomes. From this perspective, influences can be categorized as nutritional, infectious, and other environmental factors, such as pharmacological agents, toxins, and stressors. An alternative manner in which to examine the epigenetic impact and the exposome is to evaluate on a system-wide basis, such as the impact of exposomes on metabolism, brain development, and cancer risks.

**OBESITY:**

Genetic contributions to obesity have been estimated in studies of twins, non-twin siblings, and adoptees, and range from 40% to 70%.<sup>9</sup> In genome-wide association studies, numerous gene loci have been associated with obesity, with each allele variation providing but a small accounting for variations in body mass index among individuals. Investigations into the role of gene-gene or variant-variant interactions, a concept defined as epistasis wherein the effect of a gene or a variant on a trait is not independent of its effect on another gene or trait, have also failed to account for BMI variability. Recent studies in humans and in animals are providing insights into the impact of maternal, paternal and grand-parental nutrition on metabolic adaptations of the offspring.<sup>10</sup>

**DIET:**

While it is common knowledge that diet can impact obesity risk by changes in caloric intake, the exposomal role of nutrients is more nuanced. Perinatal nutrition can exert epigenetic effects via gene methylation effects on gene expression, and altered development of energy homeostatic neural pathways. To conduct studies into dietary factors, rats have been bred which were prone to diet-induced obesity (DIO), while others were diet-resistant (DR). DIO and DR breeding were conducted via epigenetic factors, such as modification of maternal nutrition. DR rats remained lean despite compelling dietary changes, such as an increasingly high-fat diet. In contrast, DIO rats defended their body weights when fed a low-fat diet through increased consumption. While DR rats indicated strong levels of leptin-responsiveness, DIO rats exhibited reduced leptin sensitivity, which could underlie the abnormal pathways predisposing to the development of obesity.

Maternal overnutrition and obesity during gestation and lactation, induced via a high-fat diet, produced obese offspring in outbred rats. With DIO rats, maternal obesity during gestation and lactation also predisposes to obesity in the offsprings. DR offspring proved more resistant to postnatal overnutrition; however, cross-fostering with DIO dams encouraged greater obesity when fed a high-fat diet.<sup>11</sup> When fostered, DR and DIO pups indicated a strong level of nutritional/ environmental influence which may encourage the expression of resistant or obesity-prone genes. Early-onset exercise together with early-onset nutrition was also subject to animal study. In DIO rats, early-onset exercise was found to ameliorate obesity. However, early-onset caloric restriction was found to encourage hoarding behavior when the pups reached adulthood, triggering increased obesity among DIO adults.<sup>12</sup>

Such animal studies of obesity, hormonal resistance, and epigenetic factors increase our understanding of human health. Animal models permit control of external variables and determination of the interplay between genetic background, perinatal factors, and the development of neural pathways. As the understanding of the intersection of epistasis and epigenetics increases, there is hope for therapeutic interventions to address obesity, and other disease epidemics which are increasing in incidence in the developed world.

**ENVIRONMENT AND NEUROBIOLOGY:**

Epigenetic factors have been shown to mediate the impact of sensory experiences on site-specific gene expression, synaptic transmission, and behavioral phenotypes. In mammals, prenatal and postnatal periods are times of rapid brain growth and maturation and constitute a window during which environmental factors can exert epigenetic modifications that influence development and long-term behaviors. The interactions between sensory experiences and the innate programs during the development of neural circuitry are at least partly modulated by epigenetic influences during the early developmental plasticity periods.

Currently serving as a surrogate for human studies, animal studies are analyzing the impact of the integration of afferent signals on specialized neurons which impact intake, assimilation, and expenditure of energy. Key hormones are transmitted across the blood-brain barrier and interact with metabolic sensing neurons. Downstream hormonal releases triggered in the paraventricular nucleus and lateral hypothalamic area increase food intake and reduce energy expenditure. Responses triggered by proopiomelanocortin neurons release alpha-melanocyte-stimulating-hormone (alpha-MSH) resulting in decreased intake and increased expenditure. This release is paired with a functional alpha-MSH antagonist, which provides a negative feedback system to inhibit intake and increase the release of leptin and insulin.<sup>10</sup> As a result, studies currently focus on epigenetic influences in such leptin and insulin production/ release factors in and their role in the development of obesity.

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## NUTRIGENOMICS AND DIET:

Findings suggest that DNA methylation and histone modifications are used to control the levels of activity of genes that might be needed for conserved core biological processes. Epigenetic effects of diet on phenotype are definitely seen in honeybees, which grow to either queenbees or workers based on diet.<sup>13</sup>

Nutrients perform critical epigenetic roles, such as DNA methylation and modification, thereby modifying genes associated with processes such as embryonic development, aging, and carcinogenesis.

Nutrients and bioactive food components may inhibit enzymes that catalyze DNA methylation or histone modifications, or alter the availability of substrates necessary for enzymatic reactions.<sup>14</sup> Folate, vitamin B-12, methionine, choline, and betaine can affect DNA methylation and histone methylation through altering 1-carbon metabolism. Two metabolites of 1-carbon metabolism can affect DNA and histones: S-adenosylmethionine (AdoMet), which is a methyl donor for methylation reactions, and S-adenosylhomocysteine (AdoHcy), which is a product inhibitor of methyltransferases. Any nutrient, bioactive component, or condition that can affect AdoMet or AdoHcy levels in the tissue can alter the methylation of DNA and histones. Vitamins such as biotin (histone biotinylation), niacin (ADP-ribosylation and histone acetylation), and pantothenic acid (acetyl-CoA histone deacetylase (HDAC)) can also play important roles in histone modifications.

Altered enzyme activity by consumed compounds may affect physiologic and pathologic processes by altering gene expression. Genistein and tea catechin affect DNA methyltransferases (Dnmt). Resveratrol, butyrate, sulforaphane, and diallyl sulfide inhibit HDAC; curcumin inhibits histone acetyltransferases (HAT). DNA methylation is catalyzed by Dnmt and regulates gene expression patterns by altering chromatin structures. By affecting Dnmt expression, nutrients and bioactive food components can change DNA methylation. Dnmts also link with enzymes toward gene expression, and shifts in gene expression may be involved in disease development. DNA demethylation is important in embryonic development and stem cell differentiation, and has not researched as well as DNA methylation. It is believed that 5-hydroxymethylcytosine (5-hmc) may serve as an intermediate in direct DNA demethylation, or serve as an intermediate. Also, 5-hmc is present in specific tissues in mammalian DNA at specific levels, encouraging further study of the role of 5-hmc in cancer and aging, where significant DNA hypomethylation is demonstrated.

Nutrients perform critical roles in DNA methylation. Folate carries a methyl group which is delivered for the synthesis of AdoMet. Methionine, choline, betaine,

vitamin B-12, and environmental factors also act as methyl donor nutrients. In animal studies, dietary folate positively correlated with genomic and p16 promoter methylation status, and altered p16 gene expression levels in aged mouse colons. In a human study, culturing of T lymphocytes with a low folate and methionine medium led to DNA demethylation and overexpression of genes associated with autoimmunity after 50 years of age as well as young participants via Dnmt1 knockdowns in T-lymphocytes. For this reason, Dnmt levels and low dietary methyl donor nutrients synergistically coordinate to alter DNA methylation and DNA methylation-mediated gene expression.

Folate is essential for DNA reprogramming in the early embryonic period, and folate deficiency is associated with neural tube defects. Children of mothers using folic acid supplementation during pregnancy had a higher rate of methylation than children not exposed to folic acid supplementation, which may affect programming of growth and development throughout life. Animal studies indicate that methyl nutrients in the periconceptual period can change DNA methylation in offspring and modify adult health-related phenotypes. In animal studies, post-weaning dietary folate also affects DNA methylation and may modify downstream disease susceptibility.

Vitamin B-12 deficiencies were seen to induce promoter hypomethylation and allied gene transcription in rats, which was not reversed by direct administration of methionine. Maternal choline availability is essential for fetal neurogenesis; in a mouse study, choline deficiency caused hypermethylation of a specific site on a gene important in hippocampal development, as well as increased expression of the gene itself. Together, the findings from the mouse study suggest that choline deficiency may change DNA methylation and alter fetal brain development. In rats, moderate maternal dietary protein restriction altered offspring phenotypes through manifestations including hypertension, dyslipidemia, and impaired glucose metabolism. However, such health outcomes can be reversed through folate supplementation.

Maternal ethanol ingestion encourages an altered adult phenotype by altering embryonic epigenotype. In an animal study of gestational alcohol exposure, changes in expression of Agouti viable yellow (Agy) occurred in the offspring of mothers ingesting ethanol and resulted in a change in coat-color among the offspring mice.

## HISTONE MODIFICATIONS

Histone modification is an important mechanism by which epigenetic influences are exerted. Histones may be modified by methylation, acetylation, phosphorylation, biotinylation, ubiquitination, sumoylation, and ADP-ribosylation via modifications at tails consisting of 15-

38 amino acids. Histone acetylation is balanced by HAT and HDAC; histone methylation is modified by histone methyltransferases and histone demethylases. Mammalian DNA methylation is highly associated with the methylation status of histones, with methylation maintained by methyltransferases and demethylases.<sup>15</sup> Histone acetyltransferases (HAT) and histone deacetylases (HDAC) regulate the steady-state balance of histone acetylation. HDAC inhibitors have been recognized as potential cancer therapeutic agents because they induce cell cycle arrest and apoptosis. Bioactive foods that have been studied for chemopreventive potential include sulforafane (an isothiocyanate from broccoli/ broccoli sprouts), diallyl sulfide (organosulfur compound found in garlic), and butyrate (an short chain fatty acid from fiber). Resveratrol, a bioactive component in grape skins and potential activator of Sirt1, has an anti-inflammatory effect against colitis and colitis-associated colon cancer.

Histone acetyl transferases (HATs) are novel molecular targets for chemotherapeutic development. Because of HAT, p300/CREB-binding protein (CBP), has been associated with cancer cell growth and survival. Here, curcumin, as an inhibitor of p300/CBP HAT, is particularly promising. Curcumin promotes protease-dependent degradation of p300 and related CBP protein, inhibits the acetyltransferase activity of p300, and may be a novel compound for development of p300/CBP-specific inhibitors. Curcumin also been shown to prevent diabetes-associated renal abnormalities.

## CONCLUSION

Epigenetic studies examine environmental factors, with gene expression altered without changes in the underlying base genome. Epigenetic research into health outcomes highlights exposomal inputs, with nutrients providing key inputs in exposome/ epigenome interactions. Studies of nutrition and obesity outcomes deepen understanding of how conditions may be induced, and factors that encourage disease-resistance.

In constant evolution, epigenetic changes are required for normal development. To understand how environmental factors may be tailored toward responsive processes and health, medical research and practice continue to devolve in light of epigenetic findings, while epigenetic medicine encompasses a new branch with promising therapeutic potential. The interplay between exposomes and the genes they influence resembles an orchestra, with epistasis providing a nuanced interaction between the exposome and the gene, and between the genes themselves.

<sup>1</sup> CREB, cAMP response element-binding protein, is a transcription factor capable of binding DNA and regulating gene expression.

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<b>Nutrient</b>	<b>Food Origin</b>	<b>Epigenetic Role</b>
<b>Methionine</b>	Sesame seeds, brazil nuts, fish, peppers, spinach	SAM synthesis
<b>Folic Acid</b>	Leafy vegetables, sunflower seeds, baker's yeast, liver	Methionine synthesis
<b>Vitamin B12</b>	Meat, liver, shellfish, milk	Methionine synthesis
<b>Vitamin B6</b>	Meats, whole grain products, vegetables, nuts	Methionine synthesis
<b>SAM-e (SAM)</b>	Dietary supplement	Enzymes transfer methyl groups from SAM directly to the DNA
<b>Choline</b>	Egg yolks, liver, soy, cooked beef, chicken, veal and turkey	Methyl donor to SAM
<b>Betaine</b>	Wheat, spinach, shellfish, and sugar beets	Break down the toxic byproducts of SAM synthesis
<b>Resveratrol</b>	Red wine	Removes acetyl groups from histones, improving health (shown in lab mice)
<b>Genistein</b>	Soy, soy products	Increased methylation, cancer prevention, unknown mechanism
<b>Sulforaphane</b>	Broccoli	Increased histone acetylation turning on anti-cancer genes
<b>Diallyl sulphide (DADS)</b>	Garlic	Increased histone acetylation turning on anti-cancer genes