Review

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Obesity: epigenetic aspects

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Abstract: Epigenetics, defined as inheritable and reversible phenomena that affect gene expression without altering the underlying base pair sequence has been shown to play an important role in the etiopathogenesis of obesity. Obesity is associated with extensive gene expression changes in tissues throughout the body. Epigenetics is emerging as perhaps the most important mechanism through which the lifestyle-choices we make can directly influence the genome. Considerable epidemiological, experimental and clinical data have been amassed showing that the risk of developing disease in later life is dependent on early life conditions, mainly operating within the normative range of developmental exposures. In addition to the 'maternal' interactions, there has been increasing interest in the epigenetic mechanisms through which 'paternal' influences on offspring development can be achieved. Nutrition, among many other environmental factors, is a key player that can induce epigenetic changes not only in the directly exposed organisms but also in subsequent generations through the transgenerational inheritance of epigenetic traits. Overall, significant progress has been made in the field of epigenetics and obesity and the first potential epigenetic markers for obesity that could be detected at birth have been identified. Fortunately, epigenetic phenomena are dynamic and rather quickly reversible with intensive lifestyle changes. This is a very promising and sustainable resolution to the obesity pandemic.

Keywords: epigenetics; lifestyle; obesity.

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Introduction

Obesity is becoming an epidemic health problem. During the last years not only genetic but also, and primarily, environmental factors have been supposed to contribute to the susceptibility to obesity. Epigenetics, the study of heritable but dynamic changes to genomic function that regulate gene expression independently of DNA sequence has begun to make its mark as a new frontier (1, 2). This review summarizes the recent advances in the understanding of the role of epigenetics in obesity and offers a personally as well as globally sustainable strategy via intense lifestyle modification to this pervasive pandemic.

Epigenetics can be defined as inheritable and reversible phenomena that affect gene expression without altering the underlying base pair sequence through processes including DNA methylation, covalent histone modifications, chromatin folding and, more recently described, the regulatory action of miRNAs and polycomb group complexes. Epigenomics is the study of 'genome-wide' epigenetic modifications. Because gene expression changes are critical in both normal development and disease progression, epigenetics is widely applicable to many aspects of biological research.

Environmental epigenetic influence

Obesity is becoming an epidemic health problem. During the last years not only genetic but also, and primarily, environmental factors have been supposed to contribute to the susceptibility to obesity. The influence of environmental/lifestyle factors including nutrients and bioactive food components on epigenetic phenomena such as DNA methylation and various types of histone modifications has been extensively investigated. Because an individual's epigenetic patterns are established during early gestation and are subject to transformation by environmental factors during their lifetime, epigenetic mechanisms are very important in the development and transgenerational transmission of chronic non-communicable diseases (NCD) including obesity (3).

More than 100 protein-coding genes are controlled by genomic imprinting in humans. These atypical genes are organized in chromosomal domains, each of which is controlled by a differentially methylated 'imprinting control region' (ICR). How ICRs mediate the parental allele-specific expression of close-by genes is now becoming understood. At several imprinted domains, this epigenetic mechanism involves the action of long non-coding RNAs. It is less well appreciated that imprinted gene domains also transcribe hundreds of microRNA and small nucleolar RNA genes and that these represent the densest clusters of small RNA genes in mammalian genomes. It has been shown that imprinted small RNAs modulate specific functions in development and metabolism and perturbation of their expression contributes to disease (4).

Recent studies indicate that normal metabolic regulation during adulthood besides requiring a good balance between energy intake and energy expenditure can be also be affected by pre- and post-natal environments. In fact, maternal nutritional constraint during pregnancy can alter the metabolic phenotype of the offspring by means of epigenetic regulation of specific genes, and this can be passed on to the next generations. Studies focused on epigenetic marks in obesity have found altered methylation and/or histone acetylation levels in genes involved in specific but also in more general metabolic processes (5).

Rising and epidemic rates of obesity in many parts of the world are leading to increased suffering and economic stress from diverting health care resources to treating a variety of serious, but preventable NCD etiologically linked to obesity, particularly type 2 diabetes mellitus (T2D) and cardiovascular diseases (CVD). Despite decades of research into the causes of the obesity pandemic, we seem to be no nearer to a solution now than when the rise in body weights was first chronicled decades ago. The case is made that impediments to a clear understanding of the nature of the problem occur at many levels. There is a pressing need to create a climate of open exchange of ideas that can remove the barriers that prevent us from making material progress in solving this pressing major public health problem of the early 21st century (6).

The etiology of obesity is multifactorial, involving complex interactions among the genetic makeup, neuroendocrine status, fetal programming, and different unhealthy environmental factors, such as sedentarism or inadequate dietary habits. Despite a relatively high heritability of common, non-syndromic obesity (40–70%), the genetic variants contributing to susceptibility do not fully explain the heritability of obesity invoking the role of epigenetic processes. Perturbation in these processes are known to cause extreme forms of obesity, e.g. Prader-Willi syndrome (PWS), but have also been convincingly associated with susceptibility to obesity. Furthermore, environmental exposures during critical developmental periods can affect the profile of epigenetic marks and result in obesity (7).

Among the different mechanisms causing obesity, epigenetics, as mentioned above, has emerged as a very important determinant. Identification of those individuals who present with changes in DNA methylation profiles, certain histone modifications, or other epigenetically related processes could help to predict their susceptibility to gain or lose weight. Indeed, research concerning epigenetic mechanisms affecting weight homeostasis may play a role in the prevention of excessive fat deposition, the prediction of the most appropriate weight reduction plan, and the implementation of newer therapeutic approaches for obesity (8–11).

This underscores a revitalized search for epigenetic factors underlying the obesity pandemic because insight into the mechanisms underlying intergenerational metabolic reprogramming carries profound implications for our understanding of phenotypic variation and evolution (12, 13).

The susceptibility to obesity and its sequelae within obesogenic environments varies greatly from one person to the next, suggesting a role for gene × environment interactions in the etiology of the disorder. Epigenetic regulation of the human genome provides a putative mechanism by which specific environmental exposures convey risk for obesity and other human diseases and is one possible mechanism that underlies the gene × environment/treatment interactions observed in epidemiological studies and clinical trials. The concept of 'lifestyle' that influences epigenetic mechanisms includes different factors such as nutrition, behavior, physical activity, working habits, smoking and alcohol consumption, environmental pollutants, psychological stress, working on night shifts and much more (14, 15).

Epigenetics 'over' genetics: the critical importance of nutrition

The evidence for familial aggregation of both T2D and obesity is substantial. To date, more than 150 genetic loci have been associated with the development of monogenic, syndromic, or multifactorial forms of T2D or obesity. However, the proportion of overall trait variance explained by these associated loci is modest (~5–10% for T2D, ~2% for obesity). Some of the familial aggregation

not attributable to known genetic variation, as well as many of the effects of environmental exposures, reflects epigenetic processes (16).

Obesity is associated with extensive gene expression changes in tissues throughout the body. This situation combined with the fact that gene expression changes are thought to have associated epigenetic changes, means that the links between obesity and epigenetics will undoubtedly be vast. Much progress in identifying epigenetic changes induced by (or inducing) obesity has already been made, with candidate and genome-wide approaches. These discoveries will aid the clinician through increasing our understanding of the inheritance, development and treatment of obesity. However, they are also of great value for epigenetic researchers, as they have revealed mechanisms of environmental interactions with epigenetics that can produce or perpetuate a disease state. In a recent review the authors went over evidence for four mechanisms through which epigenetics contributes to obesity: as downstream effectors of environmental signals; through abnormal global epigenetic state driving obesogenic expression patterns; through facilitating developmental programming and through transgenerational epigenetic inheritance (17).

The human diet has undergone profound changes over recent generations and this trend is likely to accelerate in the 21st century. Innovations in food technology, new ways of producing and processing foods and the increasing use of artificial vitamins and novel ingredients are changing the human diet in ways that our dietary monitoring systems struggle to keep pace with. There is a growing awareness of the importance of diet, but little understanding of how these changes may affect the health of current and future generations. Epigenetic programming, and specifically the persistence of functional epigenetic states following nutritional exposure, is particularly relevant to this issue. Epigenetics is emerging as perhaps the most important mechanism through which diet and nutrition can directly influence the genome and there is now considerable evidence for nutritional epigenetic programming of health and the response to diet itself. A number of nutrients and food components that are changing in the human diet have been shown to produce epigenetic states that are stable across different timescales (18).

Within the last two decades, significant progress has been made in understanding the importance of epigenetic mechanisms in the regulation of gene expression as a consequence of gene-environment interactions. Nutrition, among many other environmental factors, is a key player that can induce epigenetic changes not only in the directly exposed organisms but also in subsequent generations through the transgenerational inheritance of epigenetic traits (19).

Nutrients and bioactive food components can influence epigenetic phenomena either by directly inhibiting enzymes that catalyze DNA methylation or histone modifications, or by altering the availability of substrates necessary for those enzymatic reactions. In this regard, nutritional epigenetics has been viewed as an attractive tool to prevent obesity and related NCD. Although the possibility of developing a treatment or discovering preventative measures of these diseases is exciting, current knowledge in nutritional epigenetics is limited, and further studies are needed to expand the available resources and better understand the use of nutrients or bioactive food components for maintaining our health and preventing diseases through modifiable epigenetic mechanisms (20, 21).

Epigenetic status varies in an individual from time to time, and there is increasing awareness of the importance of this variation in health and disease. Epigenetic control is central to the way in which the genome interacts with, and responds to, the environment and even potentially the way in which the genome can influence its own environment via effects on behavior. The substrates for epigenetic reactions (acetyl and methyl groups) are central to nutritional metabolism, and there is ample evidence for nutritional effects on the epigenome. The promise of nutritional epigenetics is that it will help elucidate the way in which nutrition can influence health through direct effects on the genome (22).

Back to the periconceptional period

Increasing epidemiological evidence suggests that maternal nutrition and environmental exposure early in development play an important role in susceptibility to NCD including obesity, childhood T2D and non-alcoholic fatty liver disease highlighting the interplay between modern dietary patterns and increasing abnormalities of both immune and metabolic health. The low-grade inflammation that characterizes these NCD suggests a central role of the immune system in the pathogenesis of these conditions. Understanding how environmental influences disrupt the finely balanced development of immune and metabolic programing is of critical importance. Diet-sensitive pathways are likely to be crucial in these processes. Epigenetic mechanisms provide a strong explanation of how nutritional exposures can affect the fetal gene expression and subsequent disease risk. Although

modern dietary changes are complex and involve changing patterns of many nutrients, there is also interest in the developmental effects of specific nutrients such as folic acid levels, which have clear epigenetic effects on programming. Epigenetic modifications provide a potential link between the nutrition status during critical periods in development and changes in gene expression that may lead to disease phenotypes. An increasing body of evidence from experimental animal studies supports the role of epigenetics in disease susceptibility during critical developmental periods, including the periconceptional, gestation, and early postnatal periods. The rapid improvement in genetic and epigenetic technologies is allowing comprehensive investigations of the relevance of these epigenetic phenomena in NCD including obesity (23, 24).

Rapidly growing evidence links maternal lifestyle and prenatal factors with serious health consequences and diseases later in life. Extensive epidemiological studies have identified a number of factors such as diet, stress, gestational diabetes, exposure to tobacco and alcohol during gestation as influencing normal fetal development. In light of recent discoveries, epigenetic mechanisms such as alteration of DNA methylation, chromatin modifications and modulation of gene expression during gestation are believed to possibly account for various types of NCD (25).

Another revelation has been that obesity results when individual predisposition to deal with a restrictive environment, as engraved by genetics and/or early life experience, is confronted with an environment of plenty via a crosstalk between hypothalamic and cortico-limbic circuitry that could well be mediated via epigenetics (26).

Epigenetic 'signatures' of obesity – developmental origins of health and disease

Methylation of appetite-related genes can serve as a useful biomarker to predict weight regain after an energy restriction program. Lower methylation levels of POMC CpG sites +136bp and +138bp were associated with success in weight-loss maintenance, whereas lower total methylation levels in NPY promoter were associated with higher risk of weight regain. Therefore, the study of leukocyte methylation levels can reflect a putative epigenetic regulation of NPY and POMC, which might be implicated in the weight regain process and be used as biomarkers for predicting weight regain after dieting (27). DNA methylation in peripheral blood leukocytes of lean and obese adolescents, comparing methylation patterns between the two groups has identified two genes that are differentially methylated, both of which have roles in immune function (28).

The molecular signatures of epigenetic regulation and chromatin architectures are fundamental to genetically determined biological processes. Covalent and post-translational chemical modification of the chromatin template can sensitize the genome to changing environmental conditions to establish diverse functional states. Recent interest and research focus surrounds the direct connections between metabolism and chromatin dynamics, which now represents an important conceptual challenge to explain many aspects of metabolic dysfunction. Several components of the epigenetic machinery require intermediates of cellular metabolism for enzymatic function. Furthermore, changes to intracellular metabolism can alter the expression of specific histone methyltransferases and acetyltransferases conferring widespread variations in epigenetic modification patterns. Specific epigenetic influences of dietary glucose and lipid consumption, as well as undernutrition, are observed across numerous organs and pathways associated with metabolism. Studies have started to define the chromatin-dependent mechanisms underlying persistent and pathophysiological changes induced by altered metabolism. Importantly, numerous recent studies demonstrate that gene regulation underlying phenotypic determinants of adult metabolic health is influenced by maternal and early postnatal diet. These emerging concepts open new perspectives to combat the rising global epidemic of metabolic disorders like obesity (29, 30).

Evidence is emerging that a substantial part of susceptibility to an obesity-related pandemic showing no signs of abatement is acquired early in life, probably owing to fetal or neonatal programming via epigenetic phenomena (31, 32). Such studies provide the foundation and framework for the relatively new field of epigenetics-based developmental origins of health and disease (DOHaD) (33). This field has extended our understanding of the role played by these developmental processes and capacities in health and disease even further by investigating the transmissible nature of developmentally programmed cardiometabolic traits to subsequent generations. In a recent review, after briefly revisiting the fundamental discoveries of first-generation DOHaD research, the author considered how recent discoveries regarding the transmissibility of developmentally-acquired traits are providing new insights into the current global cardiometabolic pandemic, and how a better understanding of developmental programming including transmissibility are

essential for the conceptualization and implementation of public health initiatives aimed at stemming this global health crisis (34).

Considerable epidemiological, experimental and clinical data have been amassed showing that the risk of developing disease in later life is dependent on early life conditions, mainly operating within the normative range of developmental exposures. This relationship reflects plastic responses made by the developing organism as an evolved strategy to cope with immediate or predicted circumstances, to maximize fitness in the context of the range of environments potentially faced. There is now increasing evidence, both in animals and humans, that such 'developmental plasticity' is mediated in part by epigenetic mechanisms (35).

Combining the knowledge of genomics with epigenomics

Integration of genome-wide association single nucleotide polymorphism and epigenomic DNA methylation data can identify potential novel genotype-epigenotype interactions within disease-associated loci, thus providing a novel route to aid unraveling common complex diseases like obesity (36). Maternal dietary fat, folic acid, protein and total energy intakes induce altered epigenetic regulation of specific genes in the offspring which are associated with altered tissue function. Passage of induced phenotypic and epigenetic traits between generations involves intergenerational modifications in the interaction between maternal phenotype and environment. The methylation of specific CpG loci in fetal tissues is associated with differential future risk of obesity and T2D. Methylation of specific CpGs in adult blood also marks differential risk of NCD. Exercise induces acute 'favorable' changes in the methylation of genes in muscle. Recent advances indicate that epigenetic variation is an important influence on interactions between nutrients and the genome, which modify disease risk. In contrast to gene-polymorphisms, epigenetic variation is dynamic and can be modified by lifestyle interventions to improve health outcomes (37).

Epidemiological studies demonstrated initially that maternal undernutrition results in low birth weight with increased risk for long-lasting energy balance disorders. As stated by the DOHaD concept, nutrient supply perturbations in the fetus or neonate result in long-term programming of individual body weight set point. Adipose tissue is a key fuel storage unit involved mainly in the maintenance of energy homeostasis. Offspring from malnourished mothers present adipose tissue with a series of alterations: impaired glucose uptake, insulin and leptin resistance, low-grade inflammation, modified sympathetic activity with reduced noradrenergic innervations, and thermogenesis. These modifications reprogram adipose tissue metabolism by changing fat distribution and composition and by enhancing adipogenesis, predisposing the offspring to fat accumulation. Subtle adipose tissue circadian rhythm changes are also observed. Inappropriate hormone levels, modified tissue sensitivity (especially glucocorticoid system), and epigenetic mechanisms are key factors for adipose tissue programming during the perinatal period (38). This can eventually lead to an increased risk of NCD including obesity developing in offspring, and that this increased risk can be heritable, with epigenetics as a mediator of disease risk in response to nutritional cues. The potential for maternal nutrition to heritably alter epigenetic states has implications for population health and adaptive evolution (39).

Epigenetic processes play a central role in regulating tissue specific gene expression and hence alterations in these processes can induce long-term changes in gene expression and metabolism which persist throughout the lifecourse (40). Although many adult diseases and morbidities associate with various early life events and programming, the morbidities of T2D, CVD, and obesity seem to be common end points of many early life events despite potential confounders (41).

The recently propounded 'maternal resource hypothesis' is based upon the fact that over the past century, socioenvironmental evolution (e.g. reduced pathogenic load, decreased physical activity, and improved nutrition) have led to cumulative increments in maternal energy resources (i.e. body mass and adiposity) and decrements in energy expenditure and metabolic control. By the late 20th century, a metabolic tipping point was reached at which the postprandial insulin response was so intense, the relative number of adipocytes so large, and inactivity so pervasive that the competitive dominance of adipocytes in the sequestering of nutrient energy was inevitable and obesity was unavoidable (42). An epigenetic basis to this hypothesis has been suggested (43).

Paternal influence counts, too

In addition to the 'maternal' interactions, there has been increasing interest in the epigenetic mechanisms through which 'paternal' influences on offspring development can be achieved. Epidemiological and laboratory studies

suggest that paternal nutritional and toxicological exposures as well as paternal age and phenotypic variation can lead to variations in offspring and, in some cases, grand-offspring development. These findings suggest a potential epigenetic germline inheritance of paternal effects (44).

Another evidence of 'paternal' epigenetic influence on obesity comes from PWS. Obesity, rather severe, is an important feature of PWS. The analysis of DNA methylation patterns across the mouse brain genome in mice carrying a deletion of the Prader-Willi syndrome imprinting center (PWS-IC) on either the maternally- or paternally-inherited chromosome shows that the PWS-IC may affect DNA methylation at these loci by directly interacting with them, or may affect methylation at these loci through indirect downstream effects due to PWS-IC deletion. These findings further suggest that PWS-IC may have a previously uncharacterized epigenetic function outside of the imprinted PWS domain (45).

Epigenetics is a dynamic process. The clinical end points associated with epigenetic phenomena can be mechanistically explicable in terms of reversible gene expression. Several important health endpoints are impacted upon by metabolic programming via epigenetics. These include the link between perinatal nutrition, nutritional epigenetics and programming at an early developmental stage and its link to a range of future health risks of NCDs including obesity. Hence, both, programming and, eventually, reprogramming can become effective tools to improve health through diet-mediated epigenetic intervention at specific developmental points (46). On these lines, it has been shown that infant weight and weight gain are associated with obesity in childhood already during the first months of life, hence, epigenetic determinants of weight gain shortly after birth may be a suitable target for prevention of obesity (47).

Long-term implications

Epigenetics plays a key role in passing the adverse effects on offspring of diabetic and/or obese mothers to the next generation. The DNA methylation of H19 is significantly higher in spermatozoa of offspring of diabetic mothers than that in spermatozoa of offspring of non-diabetic mothers. These results indicated that pre-gestational diabetes and/or obesity can alter DNA methylation in offspring spermatozoa (48).

Epigenetic mechanisms seem to be involved in the development of 'visceral adiposity'. Visceral fat is strongly associated with the development of specific obesity-related metabolic alterations. The relationship between DNA methylation and weight loss, excess body weight, or adiposity outcomes has been studied. Given the development of new sequencing and omics technologies, significantly more knowledge on epigenomics of obesity and body fat distribution will emerge in the near future (49).

Emerging revelations

It is also becoming evident that inter-individual differences in obesity-susceptibility depend on epigenetic factors. In a review, the authors focused on experimental evidence concerning dietary factors influencing obesity development by epigenetic mechanisms, reporting treatment doses and durations. Moreover, they presented a bioinformatic analysis of promoter regions for the search of future epigenetic biomarkers of obesity, including methylation pattern analyses of several obesity-related genes (*epiobesigenes*), such as *FGF2, PTEN, CDKN1A* and *ESR1*, implicated in adipogenesis, *SOCS1/SOCS3*, in inflammation, and *COX7A1 LPL, CAV1,* and *IGFBP3*, in intermediate metabolism and insulin signaling. The identification of those individuals that at an early age could present changes in the methylation profiles of specific genes could help to predict their susceptibility to later develop obesity, which may allow to prevent and follow-up its progress, as well as to research and develop newer therapeutic approaches for obesity (50). *ADRB3* DNA hypermethylation (an epigenetic modification) has recently been associated with dyslipidemia in familial hypercholesterolemia. It has been shown that epigenetic changes at the *ADRB3* gene locus might be involved in the development of obesity and its related metabolic complications (51).

Early exposure to a fat-enriched diet programs the developmental profile and thus is associated with disease susceptibility in subsequent generations. Chronic low-grade inflammation, resulting from maternal high-fat diet, is activated in the fetal environment and in many organs of offspring, including placenta, adipose, liver, vascular system and brain. The prevalence of an inflammatory response is highly associated with NCD like obesity (52).

One review focused on converging data supporting the hypothesis that, in addition to 'thrifty genotype' inheritance, individuals with obesity, T2D, and metabolic syndrome with an increased risk of CVD have suffered improper 'epigenetic programming' during their fetal/postnatal development due to maternal inadequate

nutrition and metabolic disturbances and also during their lifetime, that could even be transmitted to the next generation(s). The authors highlighted the susceptibility of epigenetic mechanisms controlling gene expression to environmental influences due to their inherent malleability, emphasizing the participation of transposable elements and the potential role of imprinted genes during critical time windows in epigenetic programming, from the very beginning of development, throughout life. Increasing our understanding on epigenetic patterns' significance and their role in development, evolution and adaptation and on small molecules (e.g. certain nutrients) that reverse epigenetic (in)activation should provide us with the means to 'unlock' silenced (enhanced) genes, and to 'convert' the obsolete human thrifty genotype into a 'squandering' phenotype (53).

Another review discussed recent advances in understanding the DOHaD in a broader life-course context. The findings indicated that such epigenetic changes are highly gene specific and function at the level of individual CpG dinucleotides. Interventions using supplementation with folic acid or methyl donors during pregnancy, or folic acid after weaning, alter the phenotype and epigenotype induced by maternal dietary constraint during gestation. This suggests a possible means for reducing risk of induced NCD including obesity (54).

Caloric restriction is recommended for the treatment of obesity, but it is generally characterized by large inter-individual variability in responses. The factors affecting the magnitude of weight loss remain poorly understood. Epigenetic factors may explain some of the inter-individual variability seen in weight-loss responses. It has been shown that both DNA methylation and gene expression are responsive to caloric restriction. This provides new insights about the molecular pathways involved in body-weight-loss as well as methylation regulation during adulthood (55).

Increasing evidence from the early nutrition programming project (EARNEST) and many other investigators demonstrates that early nutrition and lifestyle have long-term effects on later health and the risk of common NCD. Currently, three key hypotheses have been defined: the fuel mediated '*in utero*' hypothesis suggests that intrauterine exposure to an excess of fuels, most notably glucose, causes permanent changes of the fetus that lead to obesity in postnatal life; the accelerated postnatal weight gain hypothesis proposes an association between rapid weight gain in infancy and an increased risk of later obesity and adverse outcomes; and the mismatch hypothesis suggests that experiencing a developmental 'mismatch' between a sub-optimal perinatal and an obesogenic childhood environment is related to a particular predisposition to obesity and corresponding co-morbidities. Using existing cohort studies, ongoing and novel intervention studies and a basic science program to investigate those key hypotheses, EARNEST is providing the scientific foundations for evidence-based recommendations for optimal nutrition considering long-term health outcomes, with a focus on obesity and related disorders. Scientific and technical expertise in placental biology, epigenetics and metabolomics is offering understanding at the cellular and molecular level of the relationships between early life nutritional status and the risk of later adiposity. This is helping refine strategies for intervention in early life to prevent obesity (56).

Differential methylation analysis between severely obese men with and without metabolic syndrome has identified 8578 methylation probes (3258 annotated genes) with significant differences in methylation levels. Pathway analysis from differentially methylated genes identified 41 overrepresented pathways. The most over-represented pathways were related to structural components of the cell membrane, inflammation and immunity and cell cycle regulation. This study provided potential targets associated with adipose tissue dysfunction and development of the metabolic syndrome associated with obesity (57).

Pacific people (especially Micronesian and Polynesian) have some of the highest rates of obesity and diabetes in the world that largely developed since the introduction of Western culture and diet. Recent studies suggest that much of the risk relates to the excessive intake of sugar (sucrose) and refined carbohydrates, leading to a fat storage syndrome/metabolic syndrome. In a study, the authors have discussed some of the environmental, genetic and epigenetic reasons why this group might be especially prone to developing obesity and related NCD compared to other ethnic groups (58).

In recent years, there has been accumulating evidence that microRNAs are key regulator molecules of gene expression. The cellular processes that are regulated by microRNAs include cell proliferation, programmed cell death (apoptosis) and cell differentiation. Adipocyte differentiation is a highly regulated cellular process for which several important regulating factors have been discovered, but still not all are known to fully understand the underlying mechanisms. An analysis of the expression of 597 microRNAs during the differentiation of mouse mesenchymal stem cells into terminally differentiated adipocytes has shown 66 miRNAs that were differentially expressed in mesenchymal stem cell-derived adipocytes compared to the undifferentiated progenitor cells (59).

This elaborates the role of miRNA in the epigenetics of obesity.

In a study to evaluate the potential association between dietary nutrients and alterations in DNA methylation in a set of five candidate genes, including *CD14, Et-1, iNOS, HERV-w* and *TNF-α*, in a population of overweight/obese subjects, positive associations were observed between TNF-α methylation and blood levels of various subsets of cholesterol, as well as between *HERV-w* methylation and dietary intakes of β-carotene and carotenoids. TNF-α methylation showed negative associations with dietary intakes of cholesterol, folic acid, β-carotene, carotenoids and retinol. These results suggest a complex relationship among nutrient intake, oxidative stress and epigenetic DNA methylation in obesity (60).

Epigenetics can even help understand and treat NCD other than T2D and CVD, associated with obesity. A review outlined the evidence showing that the association between the reproductive pathologies and obesity is not inevitable but is potentially preventable and reversible. The epigenetic marks related to obesity could constitute a therapeutic target for the reproductive disorders associated with obesity (61).

The obesity-induced inflammation promoted by adipose tissue dysfunction is thought to be an important link between obesity and cancer. Inflammation induces an increase in free radicals and subsequently promotes oxidative stress, which may create a microenvironment favorable to the tumor development in obese persons. Therefore, obesity-related oxidative stress could be a direct cause of neoplastic transformation associated with obesity and T2D in breast cancer cells. A review focused on the role of obesity-related oxidative stress in the context of chronic inflammation and the timing of breast cancer onset and progression, thereby providing targets for preventive and therapeutic strategies in the field of obesity-related T2D and breast cancer (62, 63).

Epigenetic mechanisms can be influenced by both the quality and quantity of diet. Dietary compounds such as sulforaphane found in cruciferous vegetables and epigallocatechin-3-gallate in green tea exhibit the ability to affect DNA methyltransferase inhibition, histone modifications via histone deacetylase, histone acetyltransferase inhibition, or noncoding RNA expression. Regulation of these epigenetic mechanisms has been shown to have notable influences on the formation and progression of various NCD. It has been shown that an 'epigenetic diet' including the above compounds combined with caloric restriction can influence cellular longevity through the modulation of certain key genes that encode telomerase and p16 (64).

There is evidence for a role of the de novo DNA methyltransferase, Dnmt3a in the neurons in the paraventricular nucleus of the hypothalamus to link environmental conditions to altered energy homeostasis and development of obesity (65).

Some pharmaceutical drugs like psychotropic agents are notorious for their ability to increase fat mass in psychiatric patients. The two determinants of fat mass are the production of newly differentiated adipocytes (adipogenesis), and the volume of lipid accumulation. Epigenetic programs have a prominent role in cell fate commitments and differentiation required for adipogenesis. In parallel, epigenetic effects on energy metabolism are well supported by several genetic models. Consequently, a variety of psychotropics, often prescribed in combinations and for long periods, may utilize a common epigenetic effector path causing an increase in adipogenesis or reduction in energy metabolism. In particular, the recent discovery that G protein coupled signaling cascades can directly modify epigenetic regulatory enzymes implicates surface receptor activity by psychotropic medications. The potential therapeutic implications are also suggested by the effects of the clinically approved antidepressant tranylcypromine, also a histone demethylase inhibitor, which has impressive therapeutic effects on metabolism in the obese phenotype (66).

Summary

The phenotype of an individual is the result of complex interactions between genotype, epigenome and current, past and ancestral environment, leading to lifelong remodeling of our epigenomes. Various replication-dependent and -independent epigenetic mechanisms are involved in developmental programming, lifelong stochastic and environmental deteriorations, circadian deteriorations, and transgenerational effects. Several types of sequences can be targets of a host of environmental factors and can be associated with specific epigenetic signatures and patterns of gene expression. Depending on the nature and intensity of the interaction, the critical spatiotemporal windows and developmental or lifelong processes involved, these epigenetic alterations can lead to permanent changes in tissue and organ structure and function, or to reversible changes using appropriate epigenetic tools. Given several encouraging trials, prevention and therapy of NCD including obesity by individualized tailoring of 'optimal epigenetic lifestyle' is conceivable (67).

Expert opinion

During the entire 20th century, nutrition research experienced and amazing interest and development fueled by the initial success on the fields of malnutrition and the discovery of vitamins and other essential nutrients. During the second part of the century, it was realized that most common chronic non-infectious diseases (i.e. CVD, cancer and obesity) had a strong nutritional component. However, from the public health perspective as well as from the point of view of the individual recommendations, current recommendations for healthy nutrition resemble those provided over 100 years ago. Therefore, modern nutritional research has a great potential of still contributing to improved health for future generations, assuming that the new developments in research and technologies are applied to nutritional problems. Nutrition research must embrace state of the art epidemiology, objective food assessment tools, genomics, etc. under the umbrella of molecular nutrition research. The ultimate goals of future research in epigenomics/epigenetics, transcriptomics, proteomics, metabolomics, metagenomics, advanced biostatistics, imaging, challenge tests, and integration of all data by bioinformatics are to understand the detailed mechanisms of action for how lifestyle changes interact with the body and with the individual genomes thereby providing new tools for prevention and treatment of obesity (68).

Outlook

Overall, significant progress has been made in the field of epigenetics and obesity and the first potential epigenetic markers for obesity that could be detected at birth have been identified. Eventually this may help in predicting an individual's obesity risk at a young age and opens possibilities for introducing targeted prevention strategies. It has also become clear that several epigenetic marks are modifiable, by changing the exposure *in utero*, but also by lifestyle changes in adult life, which implies that there is the potential for interventions to be introduced in postnatal life to modify unfavorable epigenomic profiles (69).

Challenges in human nutritional epigenetics research include the problem of tissue-specific epigenomes and heterogeneity of response by epigenetic loci. However, despite the challenges involved, epigenetics will continue to evolve and provide a sustainable resolution to the pandemic of obesity (70–72).

Highlights

1. Rising and epidemic rates of obesity in many parts of the world is leading to increased suffering and economic stress from diverting health care resources to treating a variety of serious, but preventable NCD etiologically linked to obesity, particularly T2D and CVD.
2. Obesity is a complex disease with multiple well-defined risk factors. Nevertheless, susceptibility to obesity and its sequelae within obesogenic environments varies greatly from one person to the next, suggesting a role for gene × environment interactions in the etiology of the disorder.
3. Epigenetics can be defined as inheritable and reversible phenomena that affect gene expression without altering the underlying base pair sequence through processes including DNA methylation, covalent histone modifications, chromatin folding and, more recently described, the regulatory action of miRNAs and polycomb group complexes.
4. Studies focused on epigenetic marks in obesity have found altered methylation and/or histone acetylation levels in genes involved in specific but also in more general metabolic processes.
5. This underscores a revitalized search for epigenetic factors underlying the obesity pandemic because insight into the mechanisms underlying intergenerational metabolic reprogramming carries profound implications for our understanding of phenotypic variation and evolution.
6. Considerable epidemiological, experimental and clinical data have amassed showing that the risk of developing diseases like obesity in later life is dependent on early life conditions, mainly operating within the normative range of developmental exposures.
7. Integration of genome-wide association single nucleotide polymorphism and epigenomic DNA modification data can identify potential novel genotype-epigenotype interactions within disease-associated loci, thus providing a novel route to aid unraveling common complex diseases like obesity.
8. Epigenetics is a dynamic process. This makes obesity not just preventable but also treatable and even curable with intensive lifestyle modification.

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List of abbreviations

CVD	cardiovascular disease
DOHaD	developmental origins of health and disease
EARNEST	early nutrition programming project
ICR	imprinting control region
NCD	non-communicable diseases
PWS	Prader-Willi syndrome
T2D	Type 2 diabetes mellitus

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