Mini Review
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Can epigenetic expression contribute to the development of an obese phenotype?

Abstract

Human obesity results from prolonged caloric imbalance, where energy intake exceeds energy expenditure over a period of months to years. It is presumed to occur as a consequence of complex interactions between environmental and heritable factors, although the search for which specific metabolic factors or genes persist has been challenging and remains incomplete. Despite a relatively high heritability of common forms of obesity which represents between 40 to 70 % of the obese population, the identification and conformation of definitive genetic or epigenetic obesogenic variants that when activated may contribute to a susceptibility for excess weight gain have been difficult to confirm. The incidence of obesity, overweight conditions, and their close association with hypertension in the US is increasing at alarming if not epidemic proportions throughout much of Western culture and society in recent history. Despite marked advances in nutrition knowledge and practice, pharmacotherapeutic management, and life-style modifications, approximately one third of the US population is now overweight, and the resulting predicted increases in the cost of medical management of overweight and obese conditions and their commonly associated pathophysiologic sequalae are becoming burdensome to public health and to the medical community. The development of obesity in most humans typically develops gradually over a duration of months to years but occurs more rapidly in onset in most commonly studied genetic models of obesity, where it usually follows the expression of an autosomal recessive genetic trait. In humans garden variety obesity is typically attributed to a combination of incompletely defined genetically linked traits and environmental factors.

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Introduction

Obesity is a common risk factor for many metabolic diseases including diabetes, heart disease, stroke, liver disease, prone to injuries, arthritis, low self-esteem, self-harm, anxiety and even depression, causing disability and as a result posing a huge burden to health and social care services. Obesity and its related pathophysiologic sequalae are now approaching epidemic proportions in Western Society if the NHANES data accumulated over the past half century are to be believed.[1] In those studies, they considered that individuals whose body mass index (BMI) fell within the range of 25 to 29.9 to be overweight, and those whose BMI exceeded 30 to be obese. The etiology of human obesity is multifactorial in nature, however, and despite marked advancements in nutrition knowledge and practice, in metabolomics and pharmacotherapeutic management, definitive treatment strategies to resolve this apparent epidemic have remained elusive.[2] Indeed, Kelly et al.,[3] proposed that by the year 2030, the global burden of overweight individuals may exceed 2.16 billion people and those considered obese equal to 1.12 billion worldwide.[3] In addition, the incidence of Type 2 Diabetes Mellitus (T2D) now affects over 80% of those whose BMI exceeds the upper value of 30 on the BMI scale and poses a significant threat to the costs of medical care for T2D and its associated cardiovascular and renal complications among those affected.[4] Numerous studies indicate that there is a strong heritable familial predisposition for obesity and overweight syndromes, and that up to 40 individual metabolic traits may exist and contribute individually or in concert in the development of overweight and obese conditions.[4] These traits may explain at least in part the 40 to 70% of the heritability observed in some families.[3–5] Accordingly, identifying and clarifying a greater understanding of the heritable and metabolic factors which contribute to the genetic predisposition for excess adiposity in combination with environmental and life-style factors may prove instrumental in tackling this issue more effectively on an individual and/or a global scale. The Odds ratio of obesity as a material contributor to hypertension and other cardiovascular diseases and disorders is also significant and increases proportionally to the increases in the magnitude of the overweight obesity or obese condition.[4] Thus, the main purpose of this paper was to review and summarize the evidence in support of epigenetic contributions to the development of obesity. The authors reviewed over 100 publications derived from Google Scholar, PubMed and other sources that linked any aspect of genetics and epigenetics with obesity and cited those manuscripts which presented evidence of support.[5]

Epigenetics contributes to gene expression: Epigenetics is the study of changes in gene expression (phenotype) without changes in the underlying DNA sequence.[6] The term has been applied to processes where both heritable and transient characteristics develop, and which may be observed in a generational or multigenerational sense. In general, the focus of epigenetics is on stable changes which can be maintained across several cell generations. The specific molecular or environmental factors which contribute to such epigenetic changes in humans are unclear and only partially elucidated.[7] Riggs et al.,[7] provided a useful operational definition of epigenetics as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence."[6–8] In 2008 the consensus definition of epigenetic process was written by a consortium of geneticists and defined as a "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence".[9] In most common rodent models of obesity, where the obese trait becomes expressed in 25% of the offspring multigenerational as a result of an autosomal recessive trait provides additional evidence for an epigenetically mediated mechanism.[10,11]

Shults et al.,[12] proposed that the mechanism for specific gene identification in a specific chromosome strongly suggests that

locating some sort of a molecular digital addressing scheme must exist. Just as transfer RNA [tRNA] can match for a specific codon to deliver a specific amino acid to the transcription process in protein synthesis, it is only logical to believe that a similar scheme might be responsible for accessing genes in the massive library of information that is stored in the chromosomes and passed on to offspring from generation to generation. In the Shults et al.,[12] proposal, homeotic genes and epigenetics might then be linked by the activation of a modular "key ring" mechanism of sorts that calls on a specific group of genes for expression, perhaps in response to changes in environmental, physiologic or metabolic signals. Since the genetic code itself is a digital code, and since proteins are produced through this genetic code, we then have evidence to suggest that digital control of the genetic code is a foundation of cellular biologic and functional characteristics and likely contributes a role in the predisposition for anthropometric characteristics including excess energy storage, regional fat distribution patterns and obesity. It is obvious that we must then ask whether this format is followed deeply throughout the process of transcription and whether it can be passed on from one generation to the next.[12]

Function of homeotic genes. Homeotic genes exist that control or direct the operation of many other genes, and surround a group of positively charged histone proteins, which help to provide a protective barrier function to genetic damage to the DNA supercoils from inadvertent environmental or chemical elements.[4,13] Epigenetic marks are tissue specific markers and include DNA methylation sites and histone modifications which together can mediate biological processes such as imprinting.[12] Methylation of nucleotide residues is a widespread feature of the genome, and occurs via the addition of a methyl group (CH3) to a cytosine residue positioned adjacent to a guanine nucleotide in the nucleotide sequence, where it can controls the balance between the repression vs non-repression of gene transcription and expression.[14] Recent studies have also reported a role for DNA methylation processes in the clock theory of ageing.[14b]

As many imprinted genes are growth factors, or regulators of gene expression controlling growth throughout the lifespan, imprinting disorders often lead to many maladies and obesity occurs as one of their clinical manifestations.[4,7,8,13,14] Histone protein types are positively charged to facilitate DNA binding, and are strongly conserved in an evolutionary sense and show limited diversity in successive generations.[13] This is a message that the histones in the cell are likely crucial to the chronology of cellular development and destiny. Small changes in histone structure and function can lead to powerful mutagenic effects or even be lethal to the cell.[13] Nature's "genetic program" appears to run out at some point but decoding the histone code and epigenetic code could bring about large advances in understanding how an organism could regrow lost components and perhaps allow us to circumvent the "genetic program" that causes an organism to undergo senescence and eventually die of old age. Methylation processes play an established role in genetic expression and ageing, typically by methylating the serine residues and providing a degree of chemical protection during environmental exposure to noxious chemicals and from extremes of Reactive Oxygen Species (ROS) often generated during heightened rates of substrate metabolism.[7–9,13,14b] Genomic imprinting determines expression of alleles according to their maternal or paternal origin[15] and establishes a balance between the expression of the parental alleles influencing growth,[16] resulting in counteracting growth effects of paternal and maternal genomes[17] In addition to growth, imprinted genes are also involved in differentiation, development, viability and metabolic functions.[18]

Nuclear chromatin harbors the epigenetic mechanism: A single, coherent model of digital storage is emerging as the naturally occurring nanotechnology which we refer to as life.[12] This model is likely to contain a set of chemical messengers including some micronutrients that, when properly keyed, will locate and attach to a chromosome or DNA-dependent component at a specific site, thus allowing the cell to call on a gene as a blueprint.[13,19] Nuclear chromatin is likely the key structure that may harbor this epigenetic activation mechanism. The typical 30-nanometer diameter structure of a DNA strand may expand from a gene being copied out of a chromosome to reflect its genetic potential and is the site where we might direct our attention in detail during the process of gene expression. This could reveal the molecular biomechanism that unspools the gene for reading its primary genetic message together with its secondary epigenetic expressions. The nucleosome is most likely the proper location for this function due to its association with between 20 to 60 base pairs of nearby linker DNA.[13,19] A properly formed molecule may therefor act as the molecular key that unspools the nucleosomes. This may lead to an understanding of the basic epigenetic mechanism of expression, and thus lead to the root of the obesity linked epigenetic coding where a control gene or homeotic gene dispatches each chromosome and strongly suggests that some sort of digital addressing scheme must exist in the genetic expression of an obesogenic phenotype.[19]

Epigenetic expression of an obesogenic anthropometric phenotype: It now appears the concept is well established that the epigenetically mediated predisposition for obesity as well as for many metabolic traits include imprinting likely has a digital nature.[5–8] We know that the genetic code is a digital information storage system, but little has been learned about the detailed epigenetic expression mechanisms that result in obesity, and the chemical and biochemical language that controls the development of complex anthropometric structures and metabolic activities. An examination of the production of limbs, organs and anthropometric features shows us that some genes, known as homeotic genes, can control the expression or suppression of clusters of genes, thereby directing the formation and placement of complex structures and features. A similar or analogous process likely exists for the expression of other anthropometric features including the predisposition for adiposity.[5–8] The similarity to subroutines in genetic computer-like programs is not likely an illusion. Single-gene mutations have been shown to have large consequences when those genes control the production of specific compounds and products of biosynthesis and metabolism including insulin sensitivity and action.[20] Those compounds may serve as "molecular addresses" that control which genes are to be influenced and to what extent at any particular time.

Due to the complex nature of anthropometric features, it seems clear that many genes must be controlled by a single or localized group of factors that may be possibly specific for that gene. This hypothesis is borne out by the fact that some single-gene mutations can completely change a limb, organ or other anthropometric characteristics.[21] When we look at the nucleosome during the copying of a gene, we must ask how the nucleosome selected that particular gene to become expressed. We also know that at any given time, not all potential genes are being expressed, so clearly there must be an underlying mechanism or process for choosing which gene to read and express and when exactly to read and express it.[19] Indeed the genes for some physiologic and anthropometric features change progressively throughout the aging and developmental processes of the normal lifespan.[22]

Obesogenic transcription loci: The 30-nanometer structure in DNA is likely not formed at random. It consists of a targeted section of DNA

that is being copied for transcription.[13–18] The huge number of genes in a chromosome indicates that the cell somehow can select a specific gene or set of genes likely compatible with survival of the organism and not act at random. If and when we can discover the mechanism for selecting the gene or cluster of genes to express, we may eventually crack the epigenetic code if for some such a thing exists as an 'epigenetic code', and thus gain a greater measure of control over cellular expression and destiny and anthropometric development. It has been suggested that this may lead to control of the internal process control language of the cell, which could lead to radical advances in controlling tissue and limb destiny and anthropometric features. In theory, this could potentially lead to regeneration of lost physiologic or metabolic processes or the ability to extend human healing and lifespan as has been suggested in some stem cell applications.[23,24]

In nature, adiposity is often considered to be a survival attribute.[25] In the animal kingdom, animals that are unable to store adequate fat stores for any reason are at greater risk of demise during periods of fast and famine during hibernation, migration, or changing environmental conditions.[23] In the simplest terms then, adiposity and excess fat accumulation occurs when energy intake exceeds energy expenditure, although individuals may respond differently to the caloric imbalance at different life stages due to genetic predisposition, physiologic processes or other factors. At an individual level, excess energy storage may occur when excessive quantities of triglycerides are generated via biosynthesis or dietary consumption, and ultimately become stored in adipose tissue depots.[26] Not all adipose tissue depots exert equivalent impact on pathophysiologic mechanisms however. Upper body fat depots reflect a greater impact on pathophysiologic sequalae, while the predominantly gender mediated contributions to lower body fat accumulations affecting the lower extremities to pathophysiologic sequelae including CVD appear minimal.[27] When metabolic needs arise, the triglycerides may be released from adipose tissue as free fatty acids (FFA), which when in excess, may provoke detrimental pathophysiologic effects such as T2D.[4] Herrera et al.,[28] have reviewed some recent evidence for genetic and epigenetic mechanisms involved in the susceptibility and development of obesity in an extensive meta-analysis. In their studies, the authors identified multiple genetic features including ethnicity, variations in body fat distribution patterns, and contributors to body mass index (BMI). It is generally accepted that BMI is a commonly cited but imperfect measure of relative fatness of an individual based solely on their height and weight.[4,29] Fat distribution varies significantly with ethnicity and gender, and admixture mapping studies demonstrate that the penetrance of obesity traits correlates closely with the percentage of ancestry derived from ethnic groups that have demonstrated an increased prevalence.[30,31]

The role of twin studies in obesity research

Bouchard and others have conducted extensive twin studies of both identical and fraternal siblings, raised together or apart.[32–34] Twin studies estimate heritability of body mass index (BMI) to be 40–70% in children and adults, and other anthropometric measures of obesity and regional fat distribution [skinfold thickness, waist circumference (WC) and waist: hip ratio (WHR)] show similar heritability.[29–38] Thus, the goals of obesity research are to elucidate pathways and epigenetic mechanisms that control deposition of excess body fat, contribute to the predisposition of obesity and its pathophysiologic sequelae, and to improve strategies for the prevention, management and therapy of obesity.

Summary and conclusion

Epigenetic markers for obesity and ageing are tissue specific and include selective DNA methylation and histone modification processes resulting in imprinting.[14b,15] These biochemical markers likely mediate finite biological processes such as epigenetic imprinting, resulting in a variable magnitude and distribution of body fat accretion in response to environmental, physiological, pathophysiological, and epigenetic factors.[14b–17] Since many imprinted genes also function as growth factors they can also act as regulators of gene expression controlling the ultimate growth, development and maturation of an organism throughout its lifespan. Of note, imprinting disorders often feature overweight obesity and obese conditions as one of their clinical manifestations.[5,15] Therefore, genomic imprinting processes determine the final expression of maternal or paternal alleles in an offspring[14] and thus establishes a balance between the expression of the parental alleles and their influence on differentiation, development, viability and metabolic processes and generational heritability.

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Conflicts of interest

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