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Mini Review

Finding Epigenetic Determinants of the Metabolic Syndrome

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Abstract

Metabolic Syndrome (MetS) substantially increases one's risk for type 2 diabetes (T2D) and cardiovascular disease. It now affects more than one third of adults in the U.S. and has similar impact on other societies globally. Results from recent genome-wide association studies (GWAS) have suggested that the inherited variance in anindividuals'risk of expressing MetS traits cannot be completely explained by variation in the primary sequence of the genome; mechanisms beyond the genetic sequence variants are increasingly compelling for researchers in the field. Epigenetic modifications such as DNA methylation and histone modifications are hypothesized to play important roles in the pathophysiology of diseases including MetS and may explain some of the missing heritability. Recent pilot studies conducted in humans and animals have also suggested epigenetic changes such as CpG methylation modify one's susceptibility to developing MetS in response to prenatal and postnatal environmental exposures. Although these findings are intriguing, more work is needed in order to unravel a map of epigenetic determinants of MetS.

Keywords: Metabolic Syndrome; DNA Methylation; Epigenetic; Obesity; Environmental Cues

Introduction

Chronic diseases such as cancer, type 2 diabetes (T2D), metabolic syndrome (MetS), cardiovascular disease and dementia constitute the most common health problems seen in developed societies (increasingly, in developing societies) and their prevalence increases with age in all populations [1-4]. It is well established that environmental exposures, especially in early life, can alter the risk of various chronic diseases later in life [5, 6] and while the mechanisms involved in this "programming" of future risk are not yet understood in detail, epigenetic changes are believed to play an important role in this process [7, 8]. Epigenetic mechanisms are also postulated to be involved in modifying the risk of MetS secondary to postnatal exposures and may explain the "missing heritability" of chronic diseases like MetS. In this mini-review, we discuss the historical context of the concept of MetS epigenetic, the recent evidence and our current opinions about this rising field.

The Metabolic Syndrome

The Metabolic Syndrome (MetS) is a form of obesity characterized by a cluster of phenotypes that includes increased abdominal fat mass, impaired insulin responsiveness, dyslipidemia with increased plasma triglycerides and decreased HDL-cholesterol, increased blood pressure and elevated circulating cytokines and adipokines [9]. It is estimated to affect 34% of adult Americans [10] and adds an extra $2,000 per person in annual health care costs [11]. Its prevalence is low in childhood and increases with advancing age [12, 13].

The prevalence of MetS-associated cardiovascular (CV) risk factors is relatively low during early childhood but increases during adolescence and thereafter tends to persist into adulthood [12-15]. We have observed a similar trend in adolescents in our cross-sectional study population [16]. It is also known that the atherosclerotic process starts in childhood and is accelerated in individuals who are insulin resistant, dyslipidemic and/or show signs of systemic inflammation [17-19]. At a molecular level, the mechanisms by which obesity leads to the development of insulin resistance, dyslipidemia and associated phenotypes are poorly understood but necessarily involve long-term changes in genetic regulation and gene expression. Since the underlying DNA sequence remains unchanged, these changes in gene regulation and function must be mediated by epigenetic mechanisms. These mechanisms, including methylation of CpG sites of DNA, are some of the most important processes by which genetic function is regulated and altered by development and by the external environment [20-26].

Why study epigenetic in MetS

Epigenetic mechanisms, which involve DNA and histone modifications, mediate the interaction between gene and environment throughout the lifespan; while the underlying genetic sequence does not change, environmental influences can alter epigenetic marks and thus alter gene expression and induce long term changes in phenotype and disease susceptibility [27]. The gradual accumulation of epigenetic changes in critical genes may contribute to the observed age-related increase in the prevalence of various chronic disorders [28-31]. Epigenetic changes are known to be heritable across more than one generation of offspring in plants and mammals [32-37] and there is evidence that transgenerational epigenetic inheritance also occurs in humans [38-41]. Such transgenerational inheritance of epigenetic states may contribute to the observed inherited risk of various chronic disorders, including metabolic disorders [42].

DNA methylation is one of the most extensively studied epigenetic mechanisms and plays an important role in the process

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of development and differentiation [43]. There is evidence from both human and animal sources that prenatal nutritional deprivation can permanently alter DNA methylation at multiple loci and these changes play a role in the observed alteration of future risk of chronic diseases like obesity, insulin resistance and diabetes [44-50]. It is also known that DNA methylation patterns continue to change after birth, at least partly in response to environmental influences [51-53]. Environmental factors can alter epigenetic features and change the future behavior of target cells and may therefore play a role in susceptibility to chronic diseases, including MetS [54-56]. In the next section, we will briefly review the role epigenetic mechanisms play in the development of MetS.

Epigenetic, prenatal exposures and MetS

Several studies have shown persistent epigenetic changes in humans who face nutritional stress during prenatal life and early childhood [45, 57-58]. Environmental exposures in early life can influence MetS phenotypes later in life through epigenetic mechanisms. Children exposed to prenatal famine and low birth weight has increased risk of T2D, hypertension and other CV disease [50, 58]. Furthermore, a large and extensive epidemiological study of humans who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–1945 showed that 60 years later they had less DNA methylation of the imprinted IGF2 gene compared with their unexposed, same-sex siblings [44].

Transgenerational epigenetic influences on MetS

Recent genome-wide association studies (GWAS) of MetS and its traits individually [59-62] revealed tens to hundreds of DNA variants that are significant but with small effect size in explaining the total heritable variance observed in each phenotype [59, 61]. Increasing evidence now shows that environment-induced genetic effects can pass transgenerationally without changes occurring in the primary DNA sequence [63] and this epigenetic trait can be transmitted up to the fifth generation [64]. Therefore, some of the familial risk of MetS may actually be epigenetic in origin. In rats, female offspring of overweight fathers (on a high fat diet) had an early onset of impaired insulin secretion and glucose tolerance that worsened with time compared to controls [42]. A recent human study showed paternal pre-conceptual obesity was associated with hypomethylation of IGF2 in newborns [40].

Global epigenetics markers are shown to be inherited from one generation to the next. In a family study conducted by McRae *et al.*, by using subjects of 117 families the authors show the average heritability of DNA methylation measured at CpG sites with no known SNPs is estimated to be 0.187 [41]. Carless et al. conducted another study in Mexican American families with high prevalence of obesity and T2D and found 24% of CpG sites tested had nominal evidence of heritabilityand the average level of heritability of these sites is 36% [65]. Some of these heritable CpGs reside within genes of known functions in metabolism [Carless M.A., personal communication]. In our family cohort of Northern European descent, we have also observed a significant portion of the epigenome is heritable, including genes known to play roles in obesity, T2D and MetS [Zhang et al., unpublished].

Postnatal transient and long-lasting epigenetic changes associated with MetS

It is also known that DNA methylation patterns continue to change after birth, at least partly in response to environmental influences [51-53]. For example, studies show that identical twins have broadly similar epigenetic profiles in-utero but these profiles gradually diverge as they get older [20, 66, 67]. Female subjects exposed to the Dutch Famine Winter when they are in young exhibited a 1.3 to 1.6 fold increased risk of type 2 diabetes as compared to unexposed women [68]. Several studies have looked at the effect of aging on genome-wide DNA methylation in adults and these studies show that age-dependent methylation changes are found in a variety of tissues and correlate well enough with age that the methylation status of selected loci can be used to predict the age of a subject [53, 69-71]. Our data show that within families at high risks for developing obesity-related metabolic disorders, there are age-associated genomic loci densely situated near genes that function in the hedgehog signaling and the maturity-onset diabetes of the young pathways (MODY) [in review]. This suggests a novel mechanism underlying the gradual deleterious effects of multiple genes and their interactions with nutrition over time, which may contribute to obesity and its complications. Our study sheds light on the relationship between ageing and increased prevalence of obesity, T2D and their related abnormalities and a dynamic epigenetic landscape that changes throughout the life span.

Exercise is an environmental factor that can also influence both DNA methylation and CV disease and obesity risk. A recent study on exercise epigenetics shows that DNA methylation of genes in retinol metabolism, calcium signaling pathways and with known functions in muscle biology and T2D decreased after exercise [72]. Some of these exercise-associated methylation changes accompanied differential gene expressions [72]. In another study using adipose tissues, 18 obesity and 21genes exhibited differential methylation at CpG loci in response to exercise.

These authors suggest exercise induces genome-wide changes in DNA methylation in human adipose tissue, potentially affecting adipocyte metabolism [73].

Conclusion

MetS has reached epidemic proportion in the last three decades and is still on the rise in essentially all populations. Epigenetic mechanisms such as genomic CpG methylation may play an important role in individual differences expressing MetS traits as these epigenetic markers are able to integrate environmental cues into gene expression.

Although it is a novel field, we see increasing amounts of interesting data supporting this theory (Figure 1).

Future Directions

More genome-wide searches for MetS relevant epigenetic variants using human populations that are well-characterized for MetS are needed to map to the interesting regions for follow-up studies. Studies that combine human sample with animal models will be instrumental in delineating the mechanisms where by identified candidates work. In both humans and animals, it will be essential to know the epigenetic states of both surrogate tissues and MetS targets

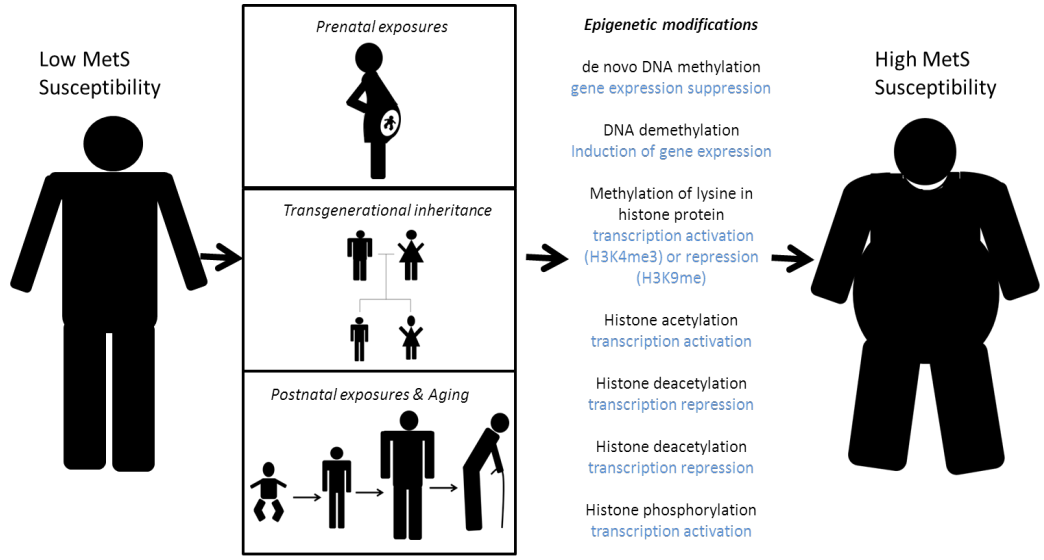

Figure 1: Epigenetic mechanisms underlying MetS etiology. Current literature supports three scenarios where epigenetic modifications may have affected an individual's susceptibility to develop MetS traits through prenatal exposures, transgenerational inheritance and postnatal exposures and aging.

such as adipose tissue, liver and muscle in relation to MetS expression. In addition, population studies using longitudinal samples as well as ones focusing on the effects of environmental cues such as diet and lifestyles will help us find novel targets for risk evaluation, diagnosis and treatment in the clinic.

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