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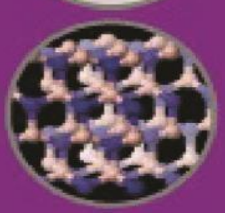


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DNA Methylation Signatures as Early Epigenetic Biomarkers of Metabolic Risk in Obesity-Mini Review

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Abstract:

Obesity is a multifactorial metabolic disorder influenced by genetic, environmental and lifestyle factors, raising the chance of developing type 2 diabetes (T2D), cardiovascular diseases and metabolic syndrome. DNA methylation in particular is one of the epigenetic mechanisms that play an important role in linking environmental exposures to changed expression of genes and metabolic dysfunction. This mini-review highlights DNA methylation's potential signatures as early biomarkers of metabolic risk in obesity. DNA methylation is the addition of methyl groups to cytosine residues altering gene expression without changing the DNA sequence. Altered methylation patterns in genes such as Leptin (*LEP*), Adiponectin (*ADIPOQ*), Proopiomelanocortin (*POMC*), Neuropeptide Y (*NPY*), Peroxisome Gamma Coactivator 1-Alpha (*PGC1Aa*) and Hypoxia Inducible Factor 3 Subunit Alpha (*HIF3A*) have been linked to insulin resistance and obesity, energy imbalance and inflammation. These changes may help identify individuals at raising the development of obesity-related metabolic complications. Furthermore, DNA methylation is potentially reversible and can be influenced by dietary modifications, physical activity and weight reduction, making it a promising target for preventive and personalised interventions. However, tissue-specific variations and differences in study populations remain challenges. Additional long-term research is needed to validate reliable DNA methylation signatures and establish their clinical utility in early metabolic risk prediction and personalised obesity management.

Keywords: Obesity, DNA Methylation, Epigenetic Biomarkers, Metabolic Risk, Insulin Resistance, Epigenetics.

INTRODUCTION

Obesity is characterised by improper or excessive fat build-up that inhibits health and contributes to the development of several co-morbidities, including type 2 diabetes (T2D), cardiovascular disease (CVD), dyslipidaemia,

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hypertension, hepatic steatosis and metabolic syndrome (MetS) (1). The complicated process of obesity is caused by interactions between environmental and behavioural conditions. As increased calorie intake and inadequate energy expenditure are key determinants, vulnerability to obesity differs considerably among individuals exposed to similar environmental situations (2-7).

The global prevalence of obesity has risen drastically over the past few decades. According to the report from WHO, the prevalence of obesity has nearly tripled since 1975. At present, even more than 1.9 billion adults (39%) are overweight, while over 650 million (13%) are classified as obese (8).

Genome-wide association reports have identified many genetic variants related with obesity. But this variant accounts for the small proportion of the observed heritability (7). Furthermore, epigenetic mechanisms may help to explain how environmental changes influence gene activity without changing the DNA sequence (9). Epigenetic mechanisms are recognised as important regulators of metabolic pathways involved in adiposity, insulin resistance and obesity related complications (10).

1. EPIGENETICS IN OBESITY

Epigenetics is defined as heritable changes in gene expression that occur without alteration in DNA nucleotide sequence and involve modification in chromatin structure that influence gene activity (11). The term epigenetics was first introduced by Conrad Waddington in 1942 to describe the interactions between genes and their environment during development (12). Over the past few decades, epigenetic regulation has emerged as a key mechanism linking genetic susceptibility with environmental influences in the development of obesity and its associated metabolic disorders.

The principal epigenetic mechanisms involved in regulating gene expression include DNA methylation, histone modification and noncoding RNAs. Among this, DNA methylation is the most extensively studied epigenetic modification in mammals because of its pivotal role in controlling gene transcription (1). This process involves the enzymatic transfer of a methyl group (-CH3) to the fifth carbon position of cytosine, producing 5-methylcytosine (13,14).

2. MECHANISM OF DNA METHYLATION IN OBESITY

DNA methylation regulates gene expression through the coordinated action of DNA methyltransferases (DNMTs), the enzymes responsible for transferring methyl groups to cytosine residues within DNA. Methylation of CpG- rich promoter regions generally represses gene transcription by preventing the binding of transcription factors and facilitating the recruitment of transcriptional repressors, including histone deacetylases (HDACs).

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Through these mechanisms, DNA methylation influences the expression of genes involved in adipogenesis, energy metabolism, insulin signalling, inflammation, and lipid homeostasis.

Altered DNA methylation can be seen either at the genome-wide level, while global DNA hypomethylation is a well-established indicator of several malignancies; its relationship with obesity remains inconsistent. Several studies have reported that global DNA hypomethylation in blood and adipose tissue samples from individuals with obesity, whereas others have reported increased global DNA methylation, resulting in the methylation pattern which may differ depending on the tissue type, study population and disease stage (15,16).

Several candidate genes involved in obesity show altered DNA methylation patterns featuring the role of epigenetic regulation in metabolic dysfunction, among these, the adipokine genes *LEP* and *ADIPOQ* are the most extensively studied because of their important role in appetite regulation, energy balance, and insulin sensitivity. DNA methylation also influences the expression of genes involved in insulin signalling, including insulin (*INS*), Insulin Receptor Substrate 1 (*IRS1*), and Phosphoinositide-3-Kinase Regulatory Subunit 1(*PIK3R1*), with an altered methylation pattern being associated with obesity and related metabolic disorders (17-19).

In addition, methylation changes in *PGC1Aa* key regulator of mitochondrial biogenesis and energy expenditure and insulin-like growth factor II (*IGF-II*), which regulates growth and metabolic homoeostasis have been reported in obesity, gestational diabetes and high-fat diet models. Especially, these epigenetic alterations may be partially reversed following restriction (20-22). Appetite-regulating genes like *POMC* and *NPY* also exhibit obesity associated methylation changes, where increased methylation of *POMC* and reduced methylation of *NPY* have been linked to weight gain and poor response to weight loss interventions. Furthermore, aberrant methylation of *HIF3A*, a gene involved in cellular adaptation to hypoxia, has consistently been related with obesity in both adults and children (23,24). Inflammatory genes such as tumour necrosis factor (*TNF)* and interleukin-6 (*IL-6)* also demonstrate altered DNA methylation in obesity, contributing to chronic low-grade inflammation and metabolic dysfunction.

3. CLINICAL SIGNIFICANCE AND FUTURE PERSPECTIVES

A possible biomarker for the early identification of metabolic risk in obese people is DNA methylation. DNA methylation marks can be used to detect the early onset of diseases, aid in diagnosis, reveal environmental exposures, and predict the likelihood of a trait or disease (25).

Unlike genetic changes, DNA methylation is reversible and can be impacted by lifestyle such as diet, physical activity, and weight loss.

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This makes DNA methylation not only a potential biomarker but also a possible target for therapeutic intervention. Several studies have shown that weight reduction and healthy lifestyle changes can partially reverse obesity-related DNA methylation changes, improving metabolic health.

Although the findings are encouraging, DNA methylation research in obesity is still evolving. Differences in age, sex, ethnicity, tissue type, and study design can affect methylation patterns, making it difficult to identify universal biomarkers. Therefore, larger studies which involves diverse populations are needed to validate these findings. Future research should concentrate on identifying reliable DNA methylation signatures that can be used in clinical practice for early diagnosis, risk prediction, and personalised management of obesity and its metabolic complications.

4. CONCLUSION

Advances in epigenetic research have improved the understanding of how DNA methylation influences obesity and its metabolic complications, offering opportunities for early diagnosis and personalised interventions. In further research, combining DNA methylation profiles with genetic, clinical and lifestyle factors may improve risk prediction and guide precision medicine approaches. However, long-term studies are still needed to validate these biomarkers and establish their routine use in clinical practice.

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